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THE PATHOLOGY OF MENINGIOMAS
A STUDY OF 121 CASES*

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Although the biologic behavior of meningiomas is relatively uniform, their histologic appearance is variable. Because of this, numerous classifications[1-7] of two fundamental types have been proposed for them: embryologic and purely morphologic.

The embryologic approach, best exemplified in the study by Globus,[5] aims at finding evidence of different stages of embryologic development of the meninges in the different appearances of the tumor. There are, however, several objections to this method. First, the origin of the meninges in neuro-ectoderm or mesoderm is still uncertain. In fact the importance of this origin probably has been over-emphasized. In discussing the classification of tumors in general, Willis[8] recently stated: "The germ-layers, the status of which has of recent years greatly declined even for the embryologist, are devoid of significance for the pathologist." Secondly, the analogy between the neoplasm and the developing meninges based on microscopic appearance is easy to make but difficult to prove. Such an idea, therefore, must remain merely an hypothesis. Lastly, the correlation between prognosis and so-called histofunctional differentiation is so poor that classifications based on embryogenetic concepts cannot be justified even on clinical grounds.

In the morphologic approach an attempt is made to classify meningiomas by the histologic features considered most prominent. Such classifications are valuable to the pathologist, but difficulties are encountered when the schemes become too complicated. This is frequently the case since, as it is well known, meningiomas are extremely polymorphic. Cushing and Eisenhardt,[6] in their morphologic classi-

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fication, thus achieved nine types subdivided into twenty variants, although they admitted that "Fine architectural distinctions, while of academic interest, are unimportant unless they can be shown to have some bearing on clinical treatment and prognosis." The latter obviously is not true of the existing classifications.

Based on a study of 121 meningiomas, it is our intention to present a new approach which affords a means for describing rather than classifying these neoplasms and in so doing sets up diagnostic criteria. The most important step in the understanding of these tumors was made by Schmidt[9] in 1902, when he discovered that the cellular structure of meningiomas was comparable to cell clusters capping the arachnoid villi and the cell nests included in the dura mater. This work unfortunately was forgotten until Cushing,[10] in 1922, re-emphasized the finding and further showed that the location of such cell nests were "favoured seats of origin" of meningiomas. The structural identity of normal arachnoid villi and the meningioma is indeed striking and offers the best criterion for recognition of the tumor. Such an origin explains why meningiomas, although arachnoidal in origin, are frequently adherent to the dura mater, but may occur in other regions such as the ventricular system or Sylvian fissure, without attachment to pachymeninges.

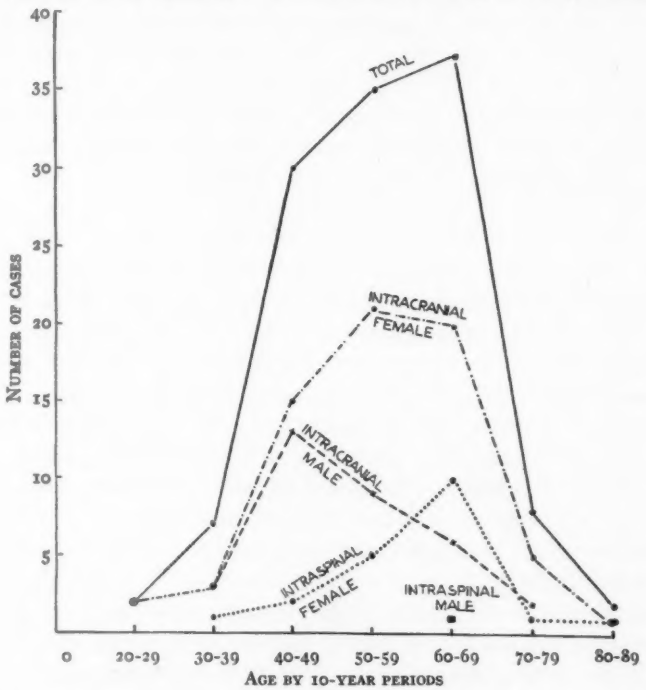
With this in mind, the description of meningiomas may be considered. These neoplasms are composed of two parts: (1) the basic cellular constituents which are meningocytic or fibroblastic cells organized at least in some places in a specific pattern known as a whorl; (2) the secondary components made up of different forms of tissue which may be absent, minimal, or prominent in the tumor. The meningeal origin of the neoplasm can be established with certainty only when some part of it contains meningocytic or fibroblastic cells arranged in a whorl pattern. The secondary components are not essential to the diagnosis although they are seen in recurrent patterns which frequently are of aid to the pathologist. The meningiomas will thus be considered using the following outline. It is emphasized that this is viewed as a description rather than as a classification.

Basic cellular constituent		*Secondary component*	
Meningocytic or Fibroblastic or Mixed	Meningioma with (or without)	fibrous psammomatous angiomatous angioblastic lipomatous osseous chondrous sarcomatous	components

Such a plan is flexible but precise and clear. Any meningioma can be defined exactly, if necessary, by addition of new components. For example, a tumor may be described as meningocytic meningioma with prominent angiomatous component. This concept not only provides rigid criteria for the diagnosis of the neoplasm but also enables the problem of differential diagnosis of other neoplasms of the meninges to be handled easily. As will be shown, these other tumors can reproduce the patterns of secondary components but do not contain the basic cellular constituents.

Material

Location, Age, and Sex (*Text-fig. 1*). Of the 121 meningiomas, 21 were situated intraspinally and 100 intracranially. It is peculiar that



Text-figure 1. Distribution of 121 meningiomas by age, sex, and location within the cranial cavity and along the vertebral canal. The age is that of the patient at the time of the first exploration, or at necropsy if not explored.

all the intraspinal tumors were located in the thoracic region except one at the sixth cervical level.

The youngest patient was 24 years old, the oldest 80. In 102 cases (84 per cent), the tumors were encountered in patients between 40

and 69 years of age, confirming the well known fact that meningiomas are seen most often in adults.

Of the 100 intracranial tumors, there were 67 in women and 33 in men, a ratio of 2:1. The predominance in females was still more striking in the spinal tumors which were present in 20 women and only one man. The peak of frequency was 10 years earlier in the males.

Duration of Symptoms. Duration is calculated as the time between the first symptom and discovery at operation. Twenty-two meningiomas (18 per cent) were discovered only at necropsy. Of the remainder, 52 (43 per cent) had a clinical duration of less than 2 years. The longest duration was 15 years. There was no relation between sex and duration.

Radiologic Signs. Only radiologic signs directly produced by the tumor are considered here, omitting manifestations of increased intracranial pressure or other diseases. Radiologic alterations were found in 24 cases (20 per cent). Condensation and hypervascularization were encountered more often than destruction of bone. These changes were most frequent in three locations: sphenoid ridge, parasagittal region, and on the convex surface of the brain.

Pathologic Anatomy

Gross Appearance and Relationship to Brain and Its Envelopes

The meningiomas were extremely variable in size. They ranged from a "pinhead" to an enormous tumor covering the entire base of the right hemisphere. The largest tumor weighed 150 gm. The tumors were well limited and generally, but not always, encapsulated. Their external surface was often granular, berry-like, or lobulated. They were gray, brown, or red; firm, soft, or mixed in consistency, and rarely sandy or calcified. Numerous dilated vessels often were seen on the surface or on the adjacent dura. Hemorrhagic or necrotic foci in mixtures of different ages were encountered. Cystic cavities were present infrequently.

Meningiomas were usually single tumors; multiple meningiomas were encountered but four times. In one instance the tumor occurred as a diffuse meningiomatosis associated with neurofibromatosis. The possibility of multiple meningiomas must be kept in mind when considering the problem of recurrences.

Attachment to the dura mater, which is one of the best means of identification of a tumor of this type at the operating table, was absent in 2 cases. In one case there was a coarsely lobulated nodule suspended by a branch of the left middle cerebral artery in the base of the Sylvian

fissure near the midline. In the second case there was a lateral intraventricular tumor.

In relation to the brain, meningiomas are generally well demarcated, but they can send finger-like expansions into the neural parenchyma.[11] In one unusual case, the tumor was large and flat, attached to the dura mater, but covering the external surface of the right hemisphere from the motor to the occipital region, forming a giant meningioma "en plaque" but without alteration of bone (Fig. 1). Frequently, the brain adjacent to the tumor is compressed. As a result, in one case the cerebral tissue which underwent cystic degeneration was removed at the first exploration and diagnosed as cystic astrocytoma of the temporal lobe. Two years later, a second craniotomy revealed a meningioma of the middle fossa. It was realized then that compression by the meningioma had produced the misleading cystic gliosis.

Basic Cellular Constituents

"Basic cellular constituents" designates the cells which resemble arachnoid cells and are arranged in a pattern similar to the arachnoid villi (Fig. 2). This appearance is the key to the histologic diagnosis of meningioma. The cells belong to two chief types: meningocytic and fibroblastic. These terms are employed because they are established by usage and clear from a descriptive standpoint, though both designate elements which are arachnoidal in origin. The cell of meningocytic type is generally the larger. The nucleus is round or oval, clear, and usually without a nucleolus. The cytoplasm is acidophilic, homogeneous or slightly granular, and frequently has ill defined boundaries so that syncytial appearances are encountered. The cell of fibroblastic type is elongated. The nucleus is slender and dark, the cytoplasm reduced to a band around it and prolonged by fibrous ends well demonstrated by silver impregnation methods. Such an appearance must be distinguished from the fibrous component (discussed later). These two types and all their intermediate appearances may be encountered in any meningioma. In addition, peculiar features sometimes are met: foamy cells with laterally placed nuclei; abnormal nuclei which are enormous, or pyknotic, or vacuolated, or contain one or two nucleoli.

The tumor cells are arranged in the specific pattern of the whorl. This pattern is more or less obvious, sometimes involving the entire tumor, in other instances being only suggested. It was present in each of the 121 meningiomas of this study. The whorl may be found in three chief forms: The first is what may be called the syncytial or plasmodial whorl (Fig. 3). This is made up of meningocytic cells

forming either large syncytial areas or small plasmodial formations resembling multinucleated cells. Often the whorl-like arrangement is not obvious and generally is more easily visible at low magnification. The second form of whorl may be called the loose-meshed whorl (Fig. 4). It is made up of fibroblastic cells attached to each other by their fibrous ends. The third form is a small concentric whorl (Fig. 5) composed of cells surrounded by concentric fibrous, acellular rings. This corresponds to the type II, variant 3 of Cushing and Eisenhardt.[6] Whorls of this kind are much less frequent than those of the first two types. Of course, all transitional forms are possible and they are often intermingled in a single neoplasm. The whorls usually are not formed around blood vessels. Though the whorl is the best evidence of a meningioma, it is not always morphologically prominent and other patterns can be demonstrated.

The next important feature is the parallel arrangement. This is made up of meningocytic or, much more frequently, of fibroblastic cells disposed in straight or curved rows. The appearance, without achieving the true palisading arrangement, can be close to that of the neurofibroma. Because of this, the differential diagnosis on occasion may be very difficult. This is especially true if it is not certain whether the tumor has any attachment to the dura or nerve root. Whorls are sometimes very rare and only suggested in a meningioma; foamy cells and macrophages, so frequent in the neurofibroma, may occur in a meningioma. There is a definite morphologic difference between the parallel arrangement of cells in a meningioma and the palisading arrangement in a neurofibroma. In the first, the cells are oval, dense, and much more uniformly distributed (Fig. 6); while, in the second, there are some areas either without cells or poorly cellular, alternating with clusters of densely packed, dark cells (Fig. 7).

The pleomorphism of meningiomas is such that many other appearances may be encountered, but these were infrequent in this series of cases. Broad sheets of meningocytic cells forming a syncytium and penetrated in places by foamy and fatty cells sometimes were seen (Fig. 9). In a few cases there was a relative absence of organization, the cells being disposed without any order in large areas (Figs 8 and 10). A "disposition stellaire" has been mentioned by Bertrand, Guillaume, and Olteanu[12] to describe this lack of cellular arrangement.

Other frequently encountered cellular arrangements include small clusters of syncytial meningocytic cells in the middle of parallel rows of cells, and large syncytial formations surrounded by narrow strands of fibroblastic cells. It is important to emphasize that no matter how

unusual the cellular pattern, the presence of a whorl establishes the definitive diagnosis. In the only 2 cases in which this structure was not found on initial examination, serial sections thereafter disclosed typical whorls (Figs. 8, 10, 12, and 15).

The Secondary Components

The secondary components are responsible in large part for the notable polymorphism of meningiomas. They may be absent, minimal, or prominent, and are mixed in exceedingly diversified ways. The presence of these components contributes also to the difficulty in diagnosis. Other tumors arising in relation to meninges may reproduce exactly the appearance of the secondary components, but do not contain the basic cellular constituents in whorl pattern.

The Fibrous Component. The fibrous component appears generally either as thick strands of fibrous tissue dividing the tumor into large islands (Fig. 11) or as a delicate network (Fig. 13). A few slender, dark cells sometimes are encountered in the fibrous tissue. In one case (Figs. 12 and 15) this component was so striking that the tumor appeared like a "fibroma" of the dura mater. The discovery of several whorls in serial sections proved it was in reality a meningioma and actually of arachnoidal origin. In 2 other cases a fibrous core was surrounded by highly cellular tissue (Figs. 14 and 16). In two tumors the fibrous component formed thick bands of fibrous tissue having the form of whorls (Fig. 17). Some arachnoid cells remained in it and for the most part it was homogeneous. The fibrous component should be distinguished from what we have called the fibroblastic part of the tumor.

The Psammomatous Component. The psammomatous component is certainly one of the most suggestive findings, without being pathognomonic. A vascular or cellular origin for this structure has been discussed frequently in the past. It is our feeling that psammoma bodies more often have a cellular origin, being the result of transformation of a whorl. The successive steps in this transformation (cellular, hyalinized, incompletely calcified, and completely calcified whorls) are well shown in Figure 18. It is possible also to find calcification in the wall or the thrombosed lumen of a vessel or in the connective tissue strands of both the dura and the fibrous component of a meningioma. But such calcification is rarely seen and often is morphologically different from psammomas, being elongated and without the characteristic onion bulb pattern. Calcific formations, when present, may be single or moderately or extremely numerous, the tumor being sandy when cut or

casting a shadow in the roentgenogram. Psammoma bodies may be confluent and form calcified masses (Fig. 20). Finally, it must be pointed out that psammoma bodies may be encountered in normal meninges or choroid plexuses.

The Vascular Component. Two kinds of vascular component are found: one frequent, the other rare. The first is called angiomatous because it is characterized by well formed, mature vessels with thin or thick walls and in places narrow or obliterated lumina (Fig. 19). These vessels are often disposed in small clusters. The angioblastic appearance is quite different and in this series was prominent only in one case (Fig. 21). The tumor contains many vascular spaces, triangular or elongated, limited by several slender cells which fill the spaces between the vessels. The appearance can mimic that of hemangioblastoma. Criteria have been given to distinguish these tumors: the almost exclusive localization of hemangioblastoma in the posterior fossa; presence of a capsule in a meningioma, but of a cyst in a hemangioblastoma. The only reliable way to make the diagnosis of meningioma, in our opinion, is to find in the tumor meningocytic or fibroblastic cells arranged in whorls.

The Lipomatous Component. The simple presence of macrophages filled with lipid material and generally found along connective tissue does not constitute the lipomatous component (Fig. 22). This is composed of adipose tissue whose cells are large and round or oval; they are optically empty, presenting a small, dark, laterally placed nucleus which is limited by a thin membrane. The fatty cells are located within the neoplastic tissue itself (Fig. 23). The presence of true fat may be confirmed by specific fat stains, since distention of the tissue by edema or by young vascular spaces may present a similar appearance. Such a true lipomatous component was found only three times, whereas macrophages with lipid material are banal. The question of a lipoma may arise in these cases, until the discovery of typical meningiomatous tissue establishes the true diagnosis.

The Osseous Component. The most frequent relation between bone and meningioma is invasion of bone by neoplastic tissue filling haversian canals (Fig. 24), the bone itself being either unaltered, or destroyed, or excited to proliferation with osteoblasts appearing in concentric lamellae. The tumor itself, however, may form osseous tissue. This was found to be the case in one instance in which bone as well as osteoblasts were present in the center of the meningioma.

The Chondrous Component. The chondrous component is a rarity. In one case, a large cartilaginous formation was present (Fig. 25).

The Sarcomatous Component. The phrase meningioma with sarcomatous component is employed to emphasize that the tumor is a meningioma as well as a sarcoma. This enables the pathologist to distinguish other malignant tumors of the leptomeninges such as diffuse sarcomatosis and melanosis which are sometimes confused with meningiomas. By "sarcomatous component" is meant the addition to typical meningiomatous tissue of some features of malignancy such as mitotic figures, abnormal nuclei, necrosis, and hemorrhages, indicating a malignant evolution, at least from the pathologic standpoint (Figs. 26 and 27). Indeed, the prognosis is not necessarily bad in these cases, and the discordance between pathologic diagnosis and clinical experience has been stressed by some authors.[6,12] This discrepancy is the chief reason for separating clearly a meningioma with sarcomatous component from a sarcoma of the meninges, the prognosis of the latter being considerably worse. Meningioma with sarcomatous component was encountered three times, a fatal outcome having occurred after 6 months in one case and after 10 months in another. The third patient is still living after 3 years.

Associated Diseases

Two cases with curious coincidental neoplasms were found. The first was a meningioma of the cerebral convexity discovered at necropsy in a female, 45 years old, who died of carcinoma of the breast with multiple metastases to cerebral dura, cerebrum, and cerebellum, and to the meningioma itself (Fig. 29). The second case was that of a meningioma of the cerebellopontine angle mingled with an ependymoma in the same location.

The classical association between multiple meningiomas and von Recklinghausen's neurofibromatosis was encountered in one instance. Small tumors of both types were numerous in this case and, peculiarly, several neurinomas were found within the spinal cord. Still more interesting in this case was the discovery of a third type of neoplastic tissue made up of large cells with stippled protoplasm and one or sometimes two lateral nuclei (Fig. 30). This tissue was intimately mixed with the meningiomatous part of a tumor arising from the falx and extending into the right cerebral hemisphere. This tissue had the appearance of a myoblastoma. Such an appearance has been seen before (Fig. 25, type I, variant 4 of Cushing and Eisenhardt[6]). It has been described as a muscular tumor by Abrikossoff[13] although it may occur in regions without muscle. Later, Leroux and Delarue[14] considered it as made up of "cellules mésenchymateuses de type histio-

cytaire." From a study of 51 cases, Fust and Custer[15] concluded that it was a special type of neurofibroma, and recently Pearse[16] interpreted it more especially as a perineural fibroblastoma. Our case is interesting because it is another example of the association between meningioma and neurofibroma, and furnishes an additional argument in favor of the neurogenic origin of the so-called myoblastoma.

Histologic and Clinical Correlations

Three components were most common in the meningiomas: fibrous, psammomatous, and angiomatous; the others were rare. There was no correlation between histologic appearance and clinical duration except for the sarcomatous component, which may be said in general to be a more rapidly growing neoplasm than the usual meningioma. The biologic behavior of meningiomas is, in fact, remarkably constant despite their polymorphism.

There was, on the contrary, some correlation between morphologic appearance and location of the neoplasm. Fibroblastic cells and parallel arrangement were prominent in tumors of the posterior fossa, in the psammomatous component in the spinal tumors, and in the meningiomas of the sphenoid ridge. Less frequently, a vascular component was found in the tumors on the cerebral convexity and in the parasagittal region. It is of interest that radiologic and macroscopic alterations of bone were most common also in those cases in which the meningiomas were on the sphenoid ridge, cerebral convexity, and in the parasagittal area.

Histologically, the important fact about these meningiomas, also stressed by previous authors, is that they were extremely polymorphic, a mixture of several of the various components having been seen in some of the tumors. An association of two sharply different types of tumor is seen in Figure 28. This demonstrates how discovery of a single component may be related to the plane of the section. These facts emphasize the difficulty in classifying meningiomas rigidly.

Summary

A new approach to the interpretation of meningiomas is suggested, based on a clinicopathologic study of 121 cases. The present concept is that meningocytic or fibroblastic cells, alone or in combination, are the basic cellular constituents of these neoplasms. The diagnosis is established by the finding of such cells in the characteristic whorl pattern. There are thus meningocytic meningiomas, fibroblastic meningiomas, and mixed types. Secondary components (lipomatous, hemangiomatous, psammomatous) may or may not be associated with these

cells. The secondary components are not essential for the diagnosis, but for descriptive purposes may be included as in "fibroblastic meningioma with mild psammomatous component." The flexibility of this scheme permits adaptation of the diagnosis to the extreme polymorphism of meningiomas. The tumor is strictly defined in morphologic terms and can be described clearly and completely.

Mr. Antol Herskovitz prepared the photomicrographs.

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[*Illustrations follow*]

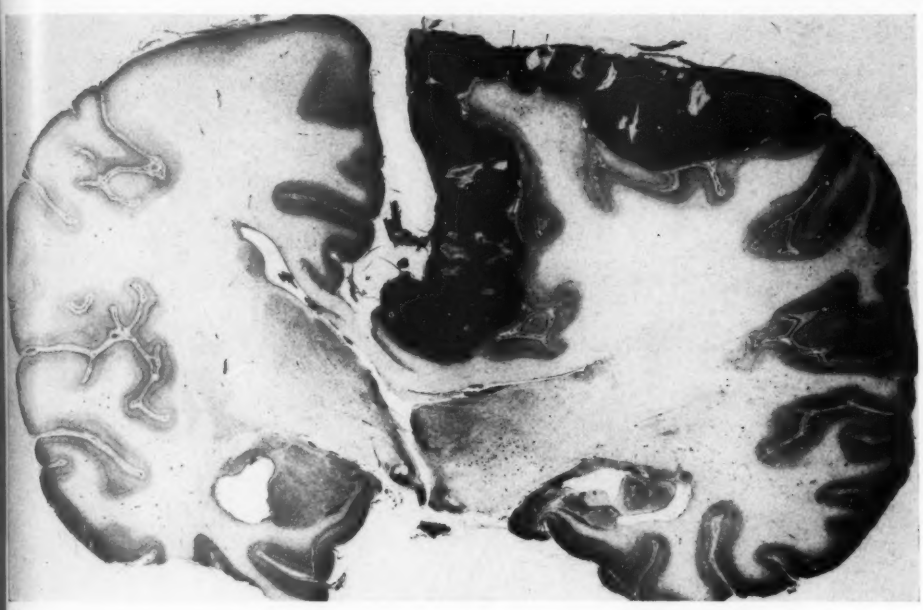
DESCRIPTION OF PLATES

All photomicrographs are of hematoxylin and eosin preparations except Figure 1 which was stained by the Nissl technic.

PLATE 108

FIG. 1. Giant meningioma shown in a coronal section of brain, extending over dorsal surface of brain and deep into the median fissure.

FIG. 2. Normal arachnoid villi in superior longitudinal sinus. × 230.



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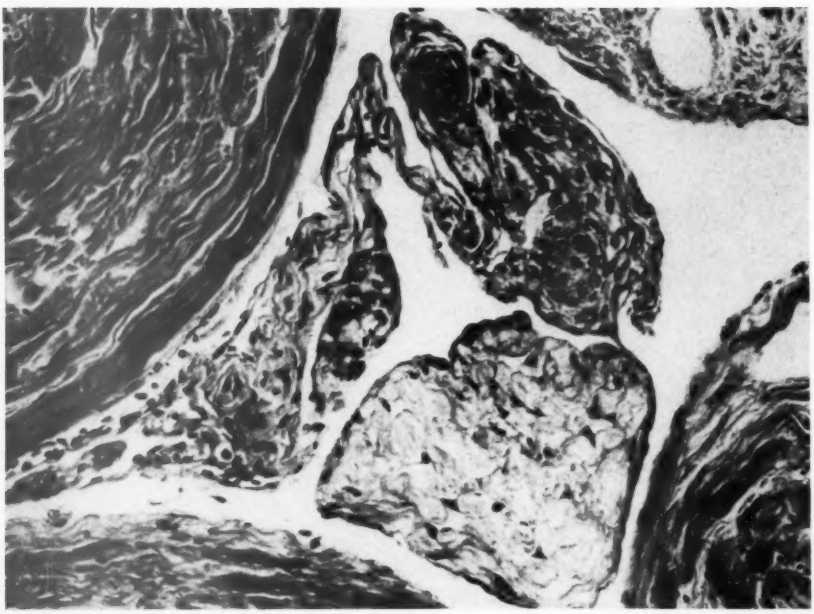

PLATE 109

FIG. 3. Syncytial whorls formed by meningocytic cells. × 550.

FIG. 4. Whorls of loose-meshed type. × 550.

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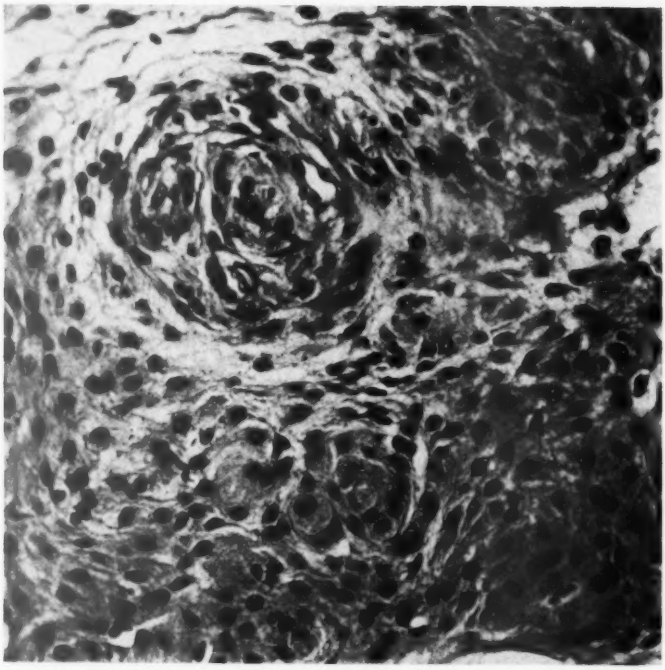

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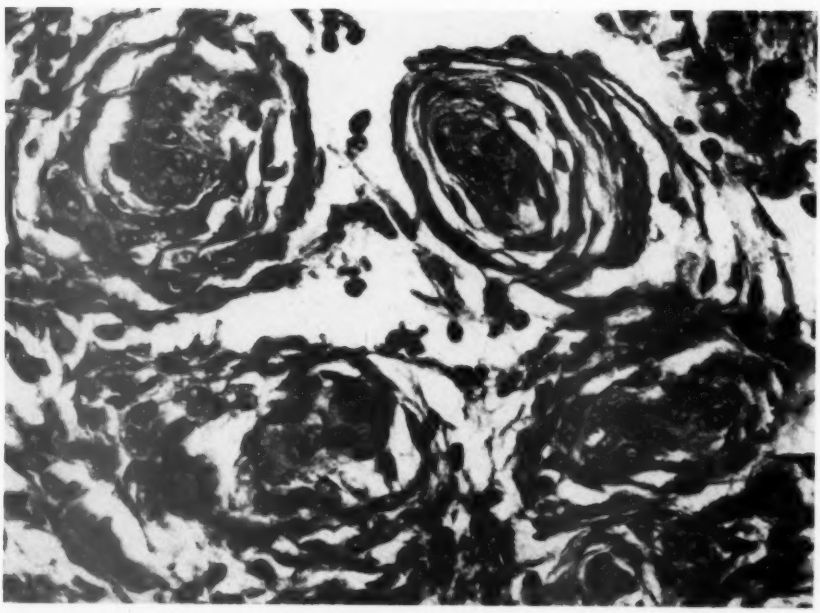
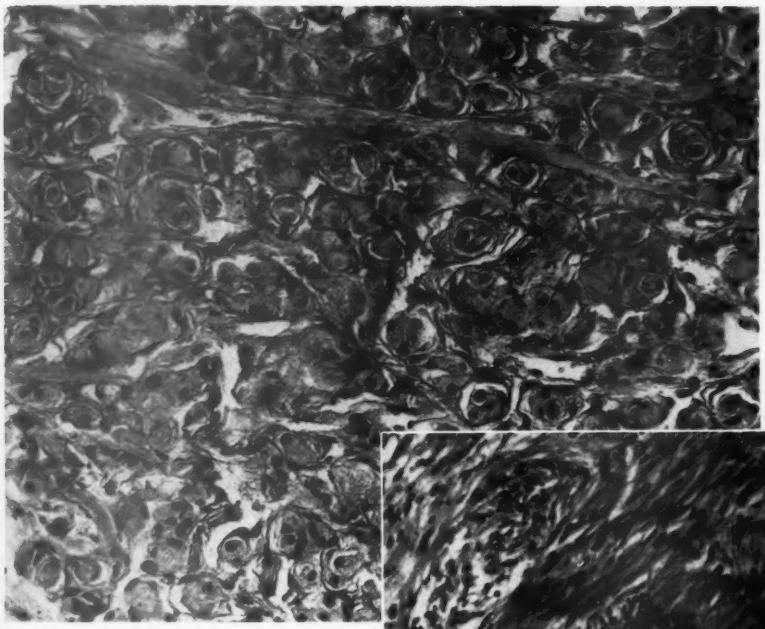


PLATE 110

FIG. 5. Whorls of concentric small type. × 150.

FIG. 6. Parallel arrangement formed by fibroblastic cells in a meningioma. × 150.

FIG. 7. Palisading arrangement in a neurofibroma. × 150.



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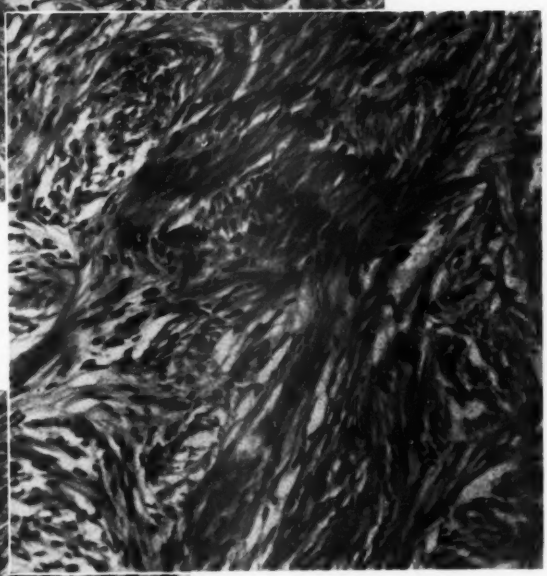

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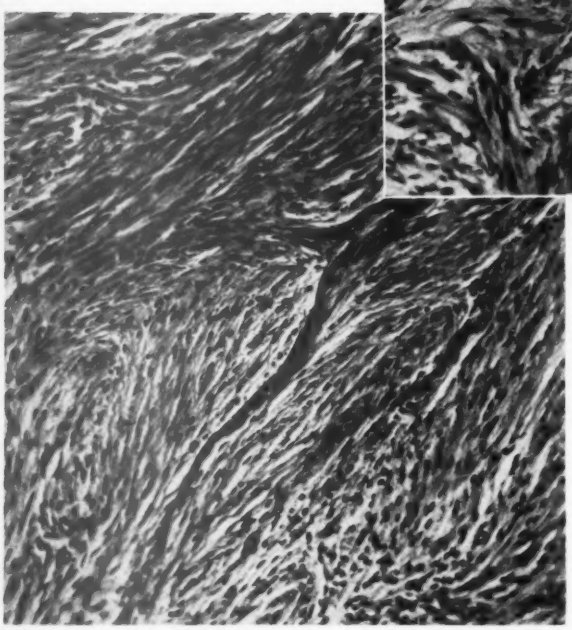

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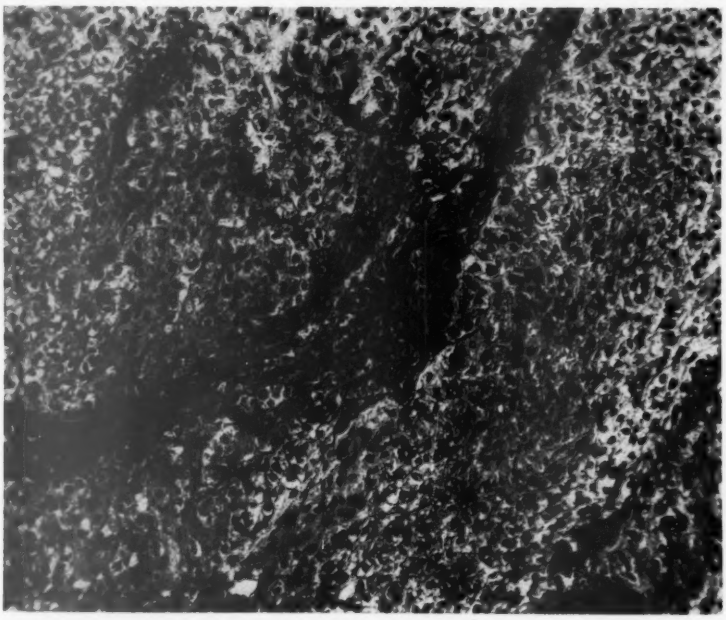
PLATE 111

FIG. 8. Meningioma of unusual type in which cells are without special organization and the tumor cannot easily be identified as a meningioma. For comparison with Figure 10. × 150.

FIG. 9. Broad sheets of meningocytic cells forming a syncytium and penetrated in places by foamy and fatty cells. Two psammoma bodies are visible. × 260.



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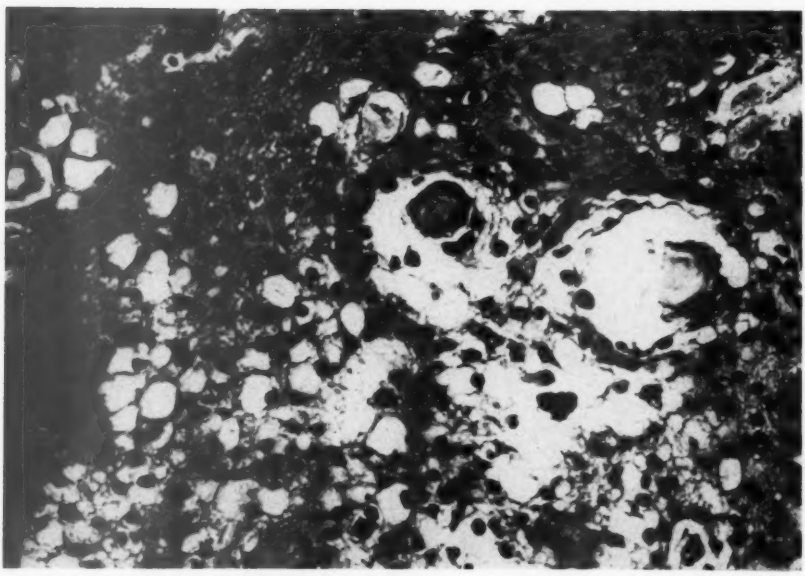

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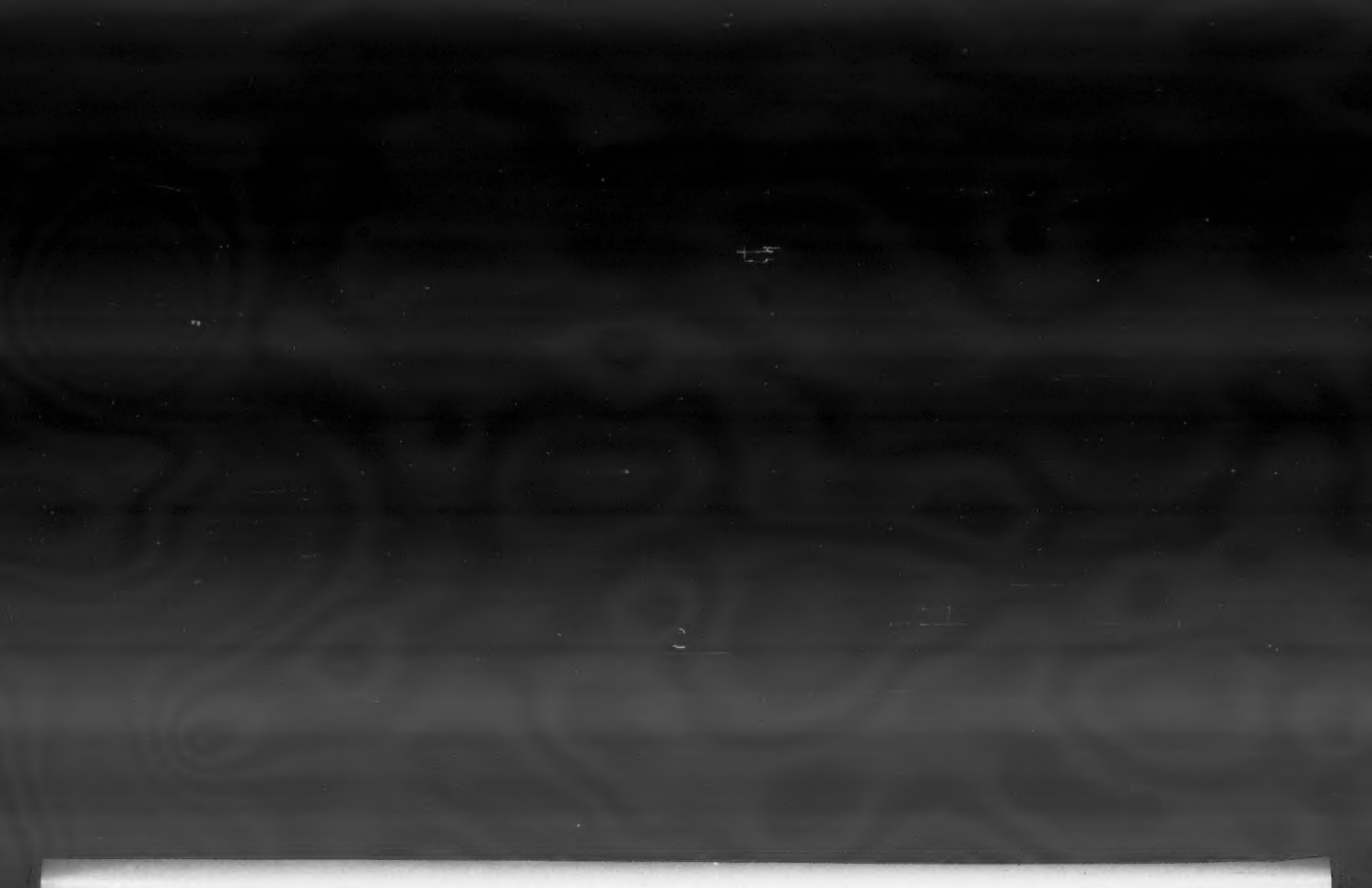
PLATE 112

FIG. 10. A portion of the tumor shown in Figure 8, found in serial sections, demonstrating two characteristic syncytial whorls. × 220.

FIG. 11. Thick strands of fibrous tissue divide the tumor cells into small islands. × 150.



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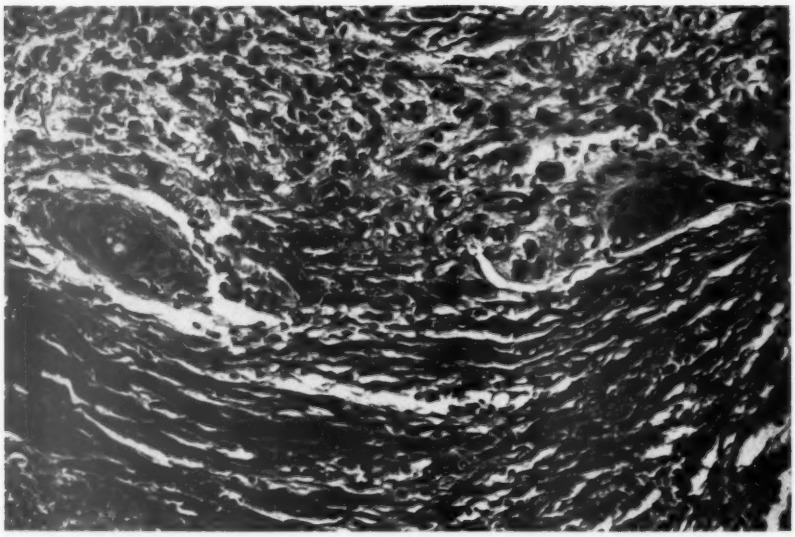

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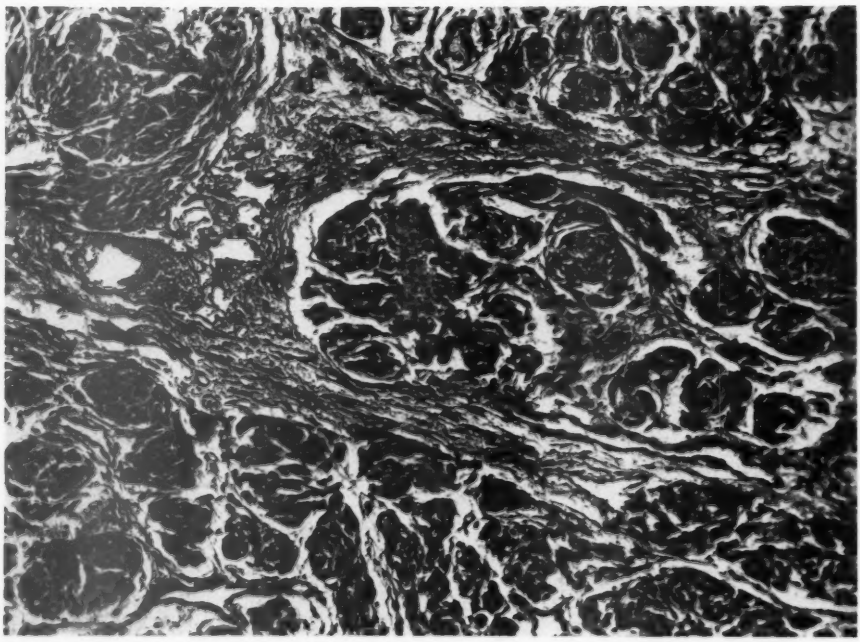

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PLATE 113

FIG. 12. Unusual type of fibrous component resembling a scar. The tumor cannot be identified easily as a meningioma. For comparison with Figure 15. × 150.

FIG. 13. Delicate network of fibrous tissue with some fibroblastic cells and slight admixture of meningocytic cells. This secondary fibrous component should not be confused with the pure fibroblastic type seen in Figure 6. × 150.

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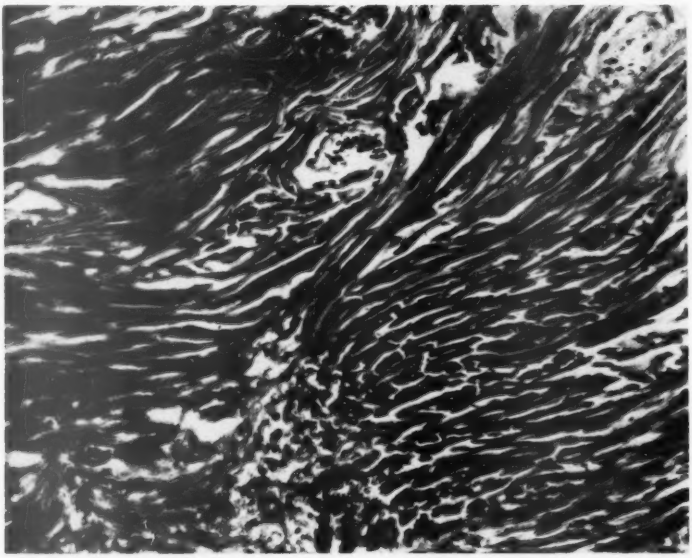

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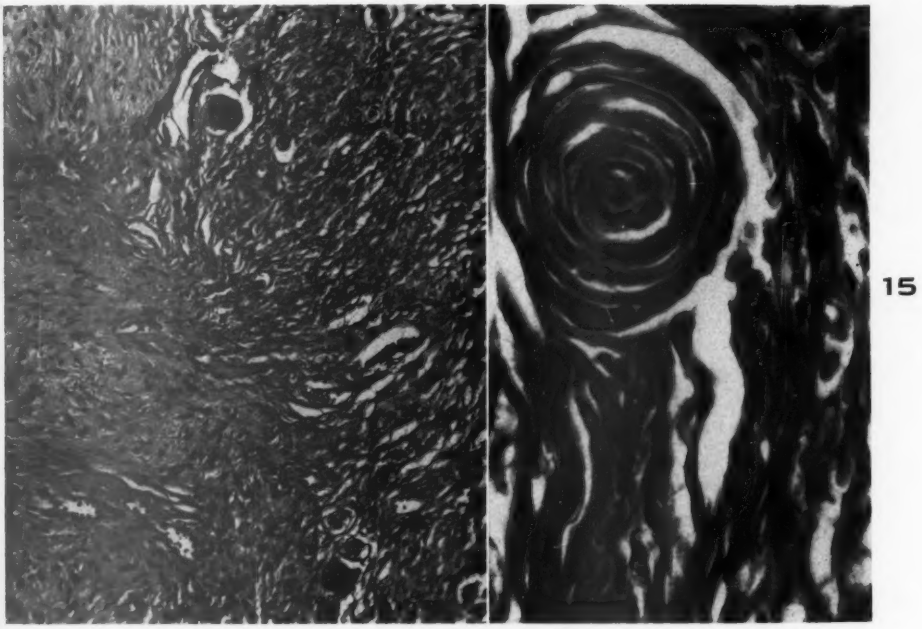
PLATE 114

FIG. 14. Higher magnification of the field shown in Figure 16, on the border of the fibrous core. × 150.

FIG. 15. A portion of the tumor shown in Figure 12, found in serial sections, demonstrating a characteristic whorl. × 700.

FIG. 16. Fibrous core in a cellular meningioma. × 22.



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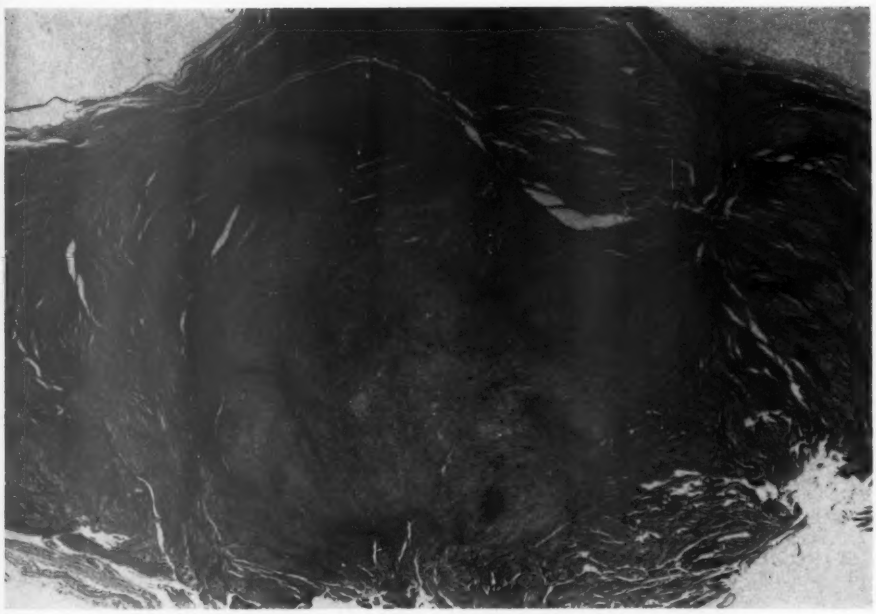

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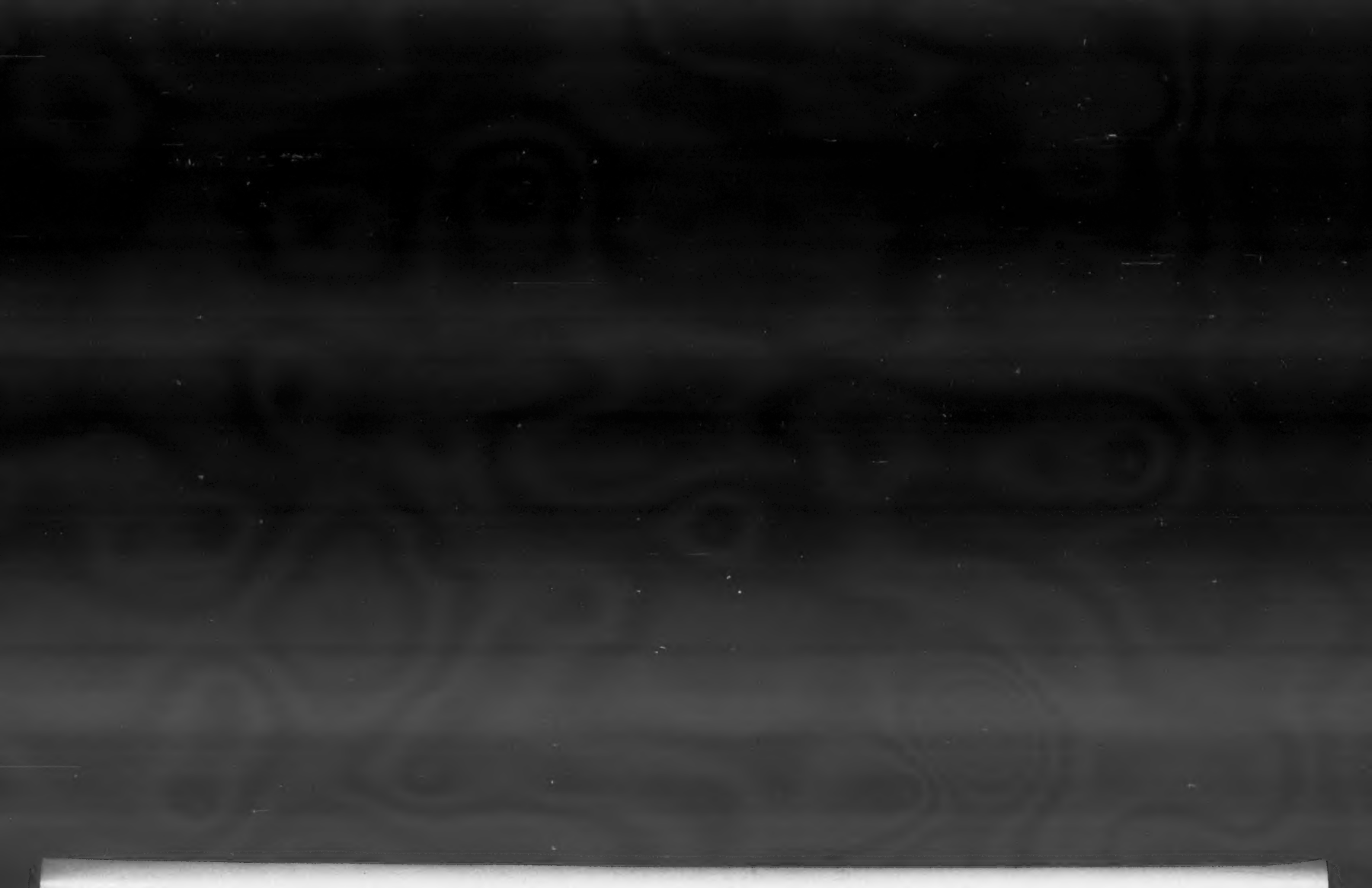
PLATE 115

FIG. 17. Thick, homogeneous, fibrous component forming whorls. × 120.

FIG. 18. The various stages of formation of psammoma bodies are shown: cellular, hyalinized, partially and completely calcified whorls. × 230.



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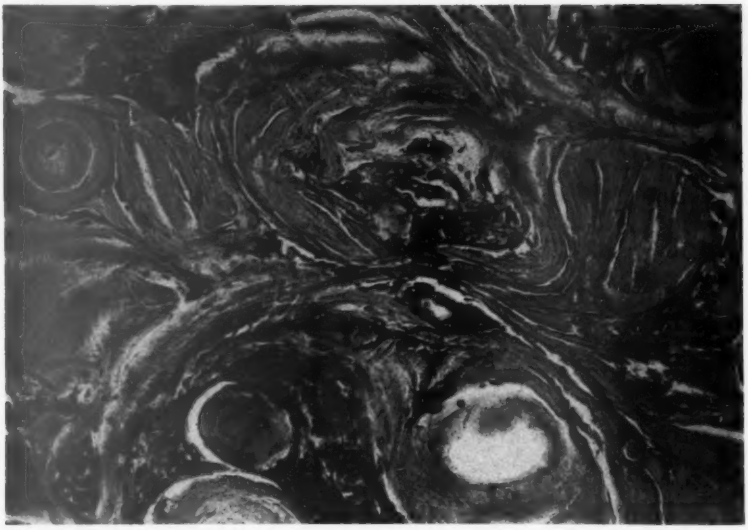

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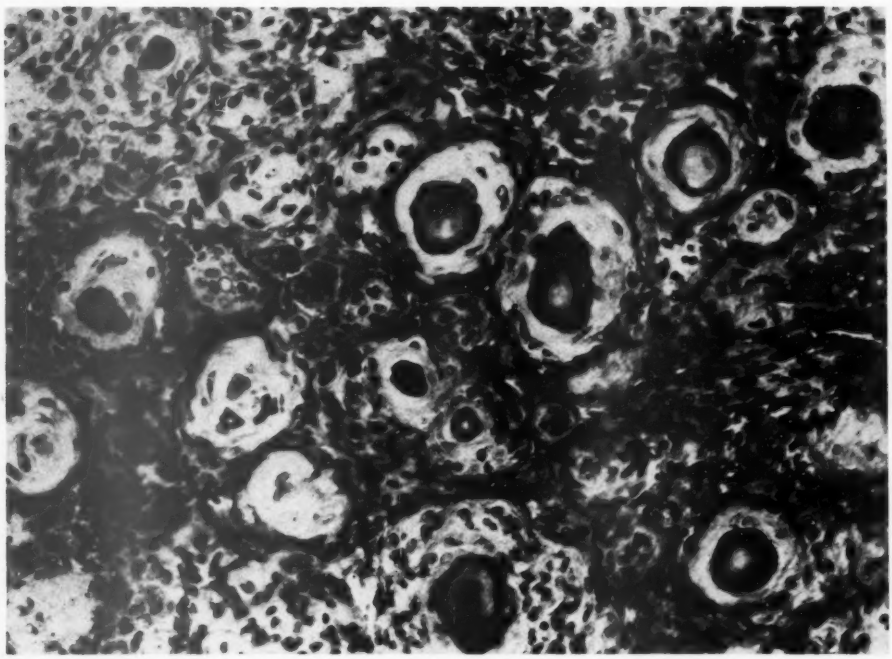

Plate 116

Fig. 19. Angiomatous component in meningocytic meningioma. × 120.

Fig. 20. Fusion of psammoma bodies to form large calcified zones. × 135.

Fig. 21. Angioblastic component formed by numerous immature vascular spaces. × 225.

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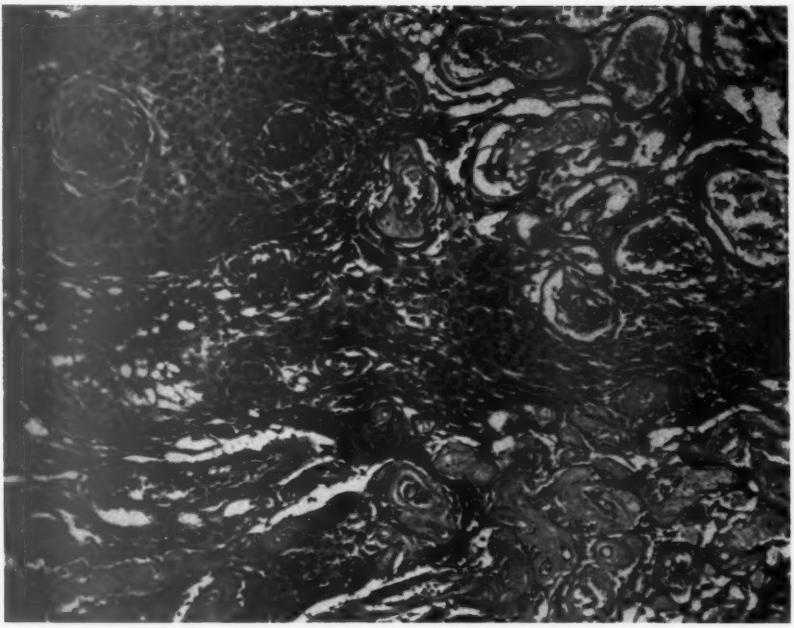

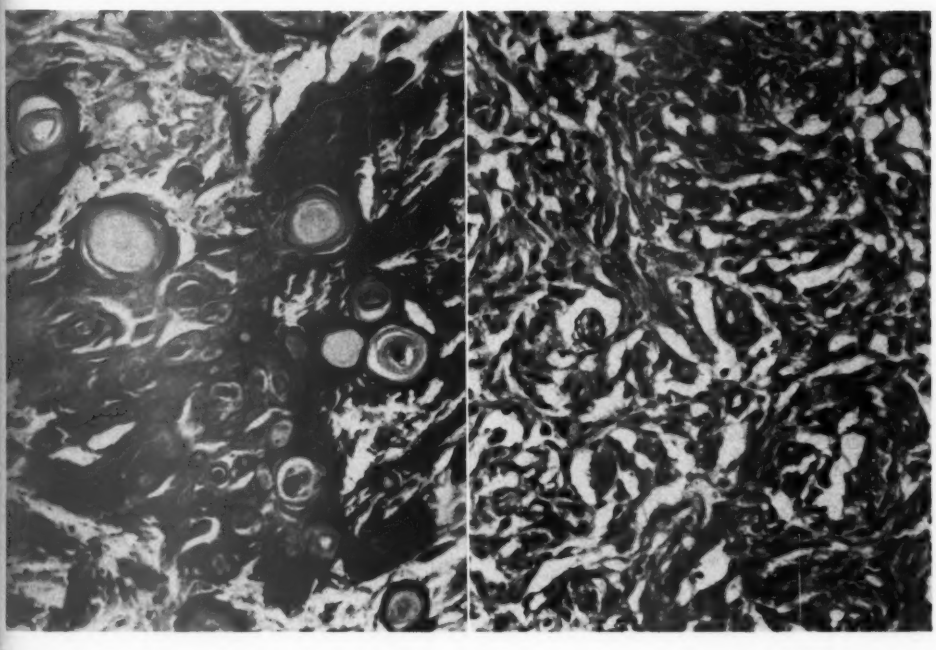

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PLATE 117

FIG. 22. Lipid-laden macrophages and lymphocytes adjacent to meningocytic meningioma. × 150.

FIG. 23. True lipomatous component in meningocytic meningioma. × 150.

FIG. 24. Invasion of haversian canals by neoplasm without alteration of surrounding bone. × 110.

FIG. 25. Chondrous component in a meningioma. × 235.

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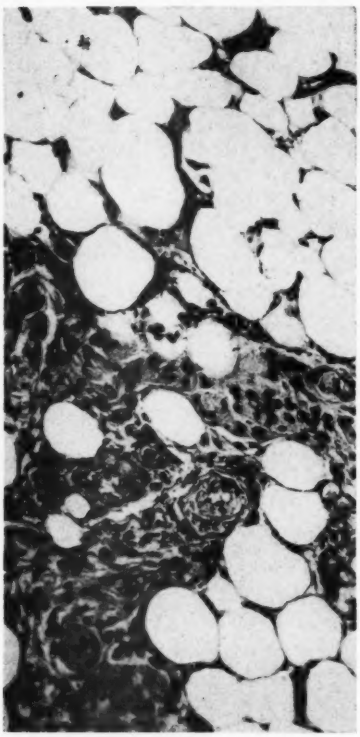

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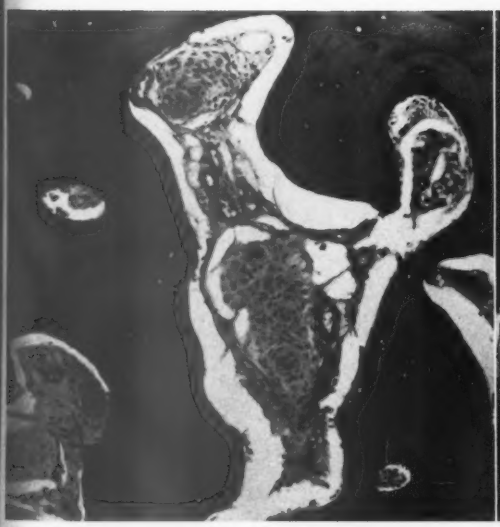

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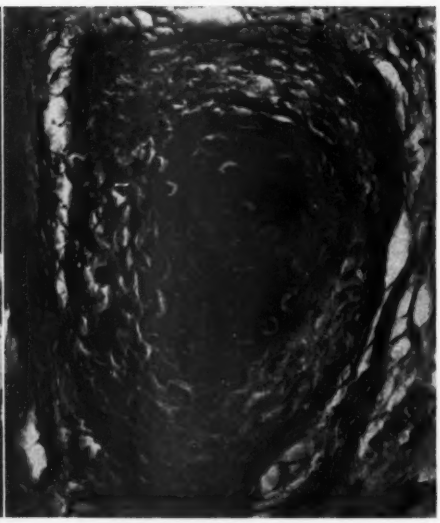

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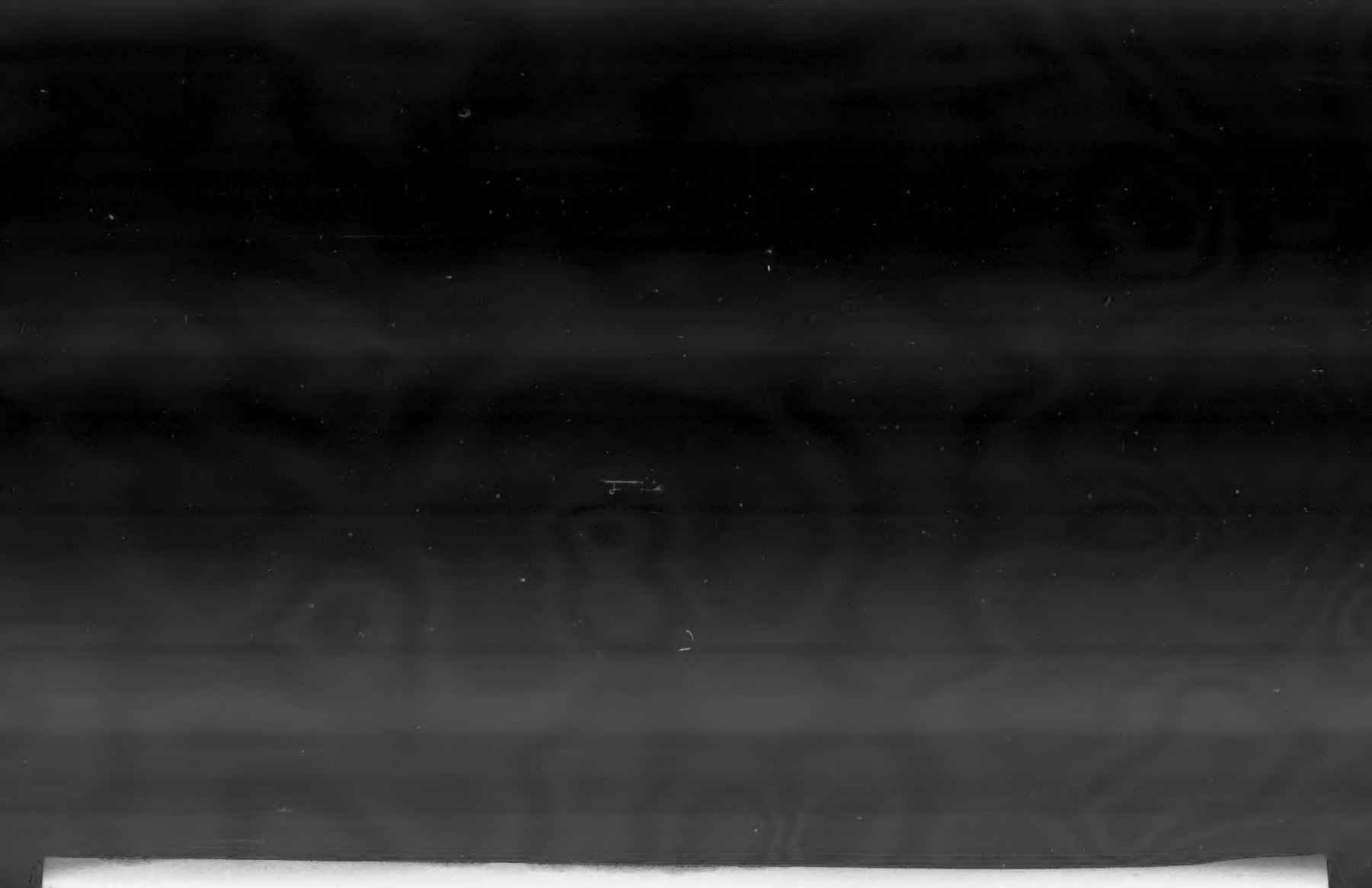
PLATE 118

FIG. 26. Focus of necrosis in sarcomatous component of a fibroblastic meningioma. Whorls and parallel arrangements of the basic cells are seen. × 150.

FIG. 27. Pseudo-palisading arrangement around another focus of necrosis in same tumor as in Figure 26. × 150.



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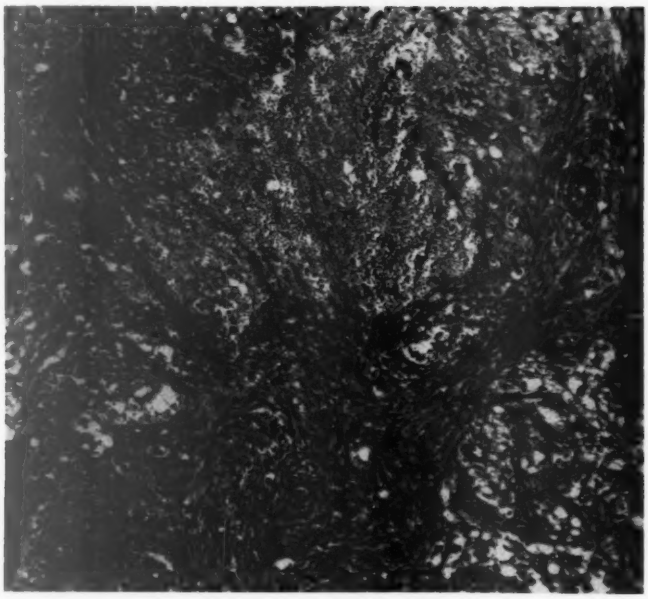

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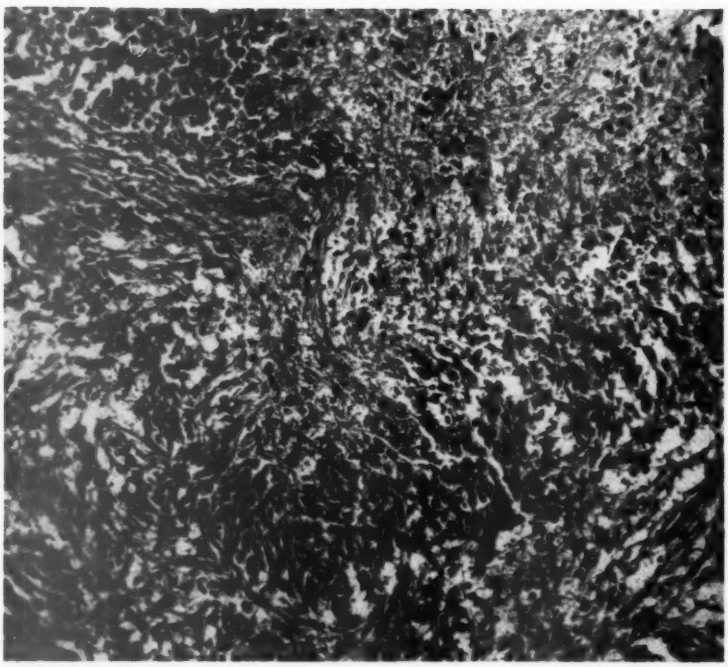
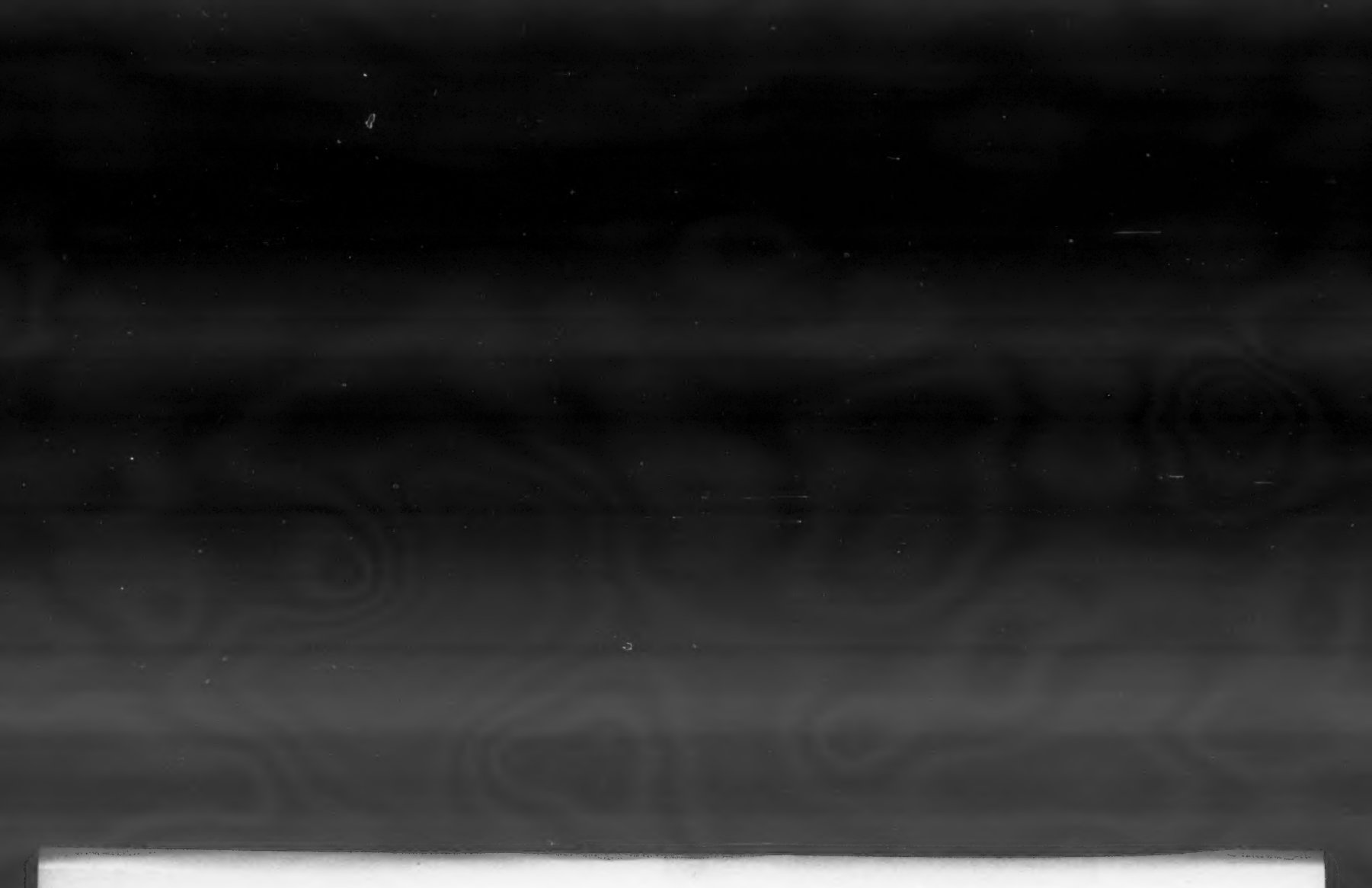


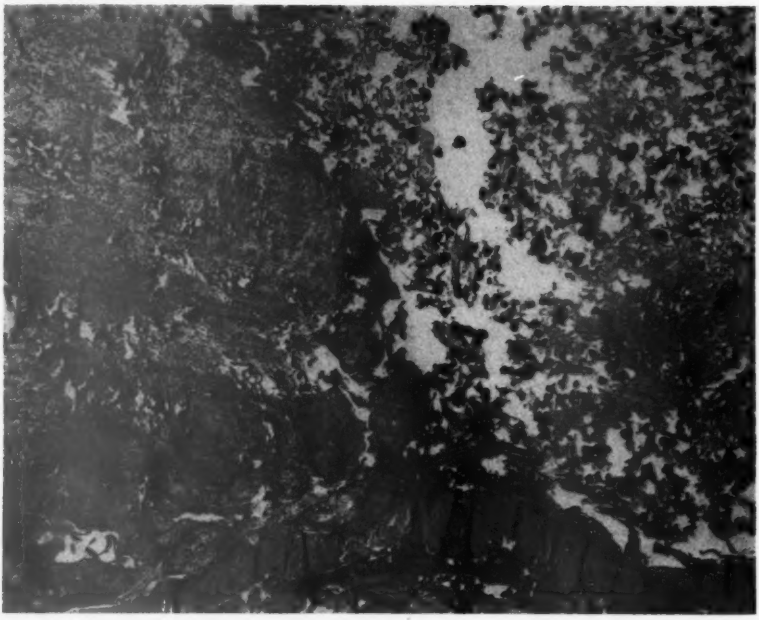
PLATE 119

FIG. 28. Two different types of meningioma in the same tumor lie sharply separated and attached to dura below. This illustrates how discovery of a single component may be a matter of chance. × 30.

FIG. 29. Metastasis of carcinoma of breast to a meningioma. × 330.

FIG. 30. Myoblastoma in association with fibroblastic meningioma. × 210.





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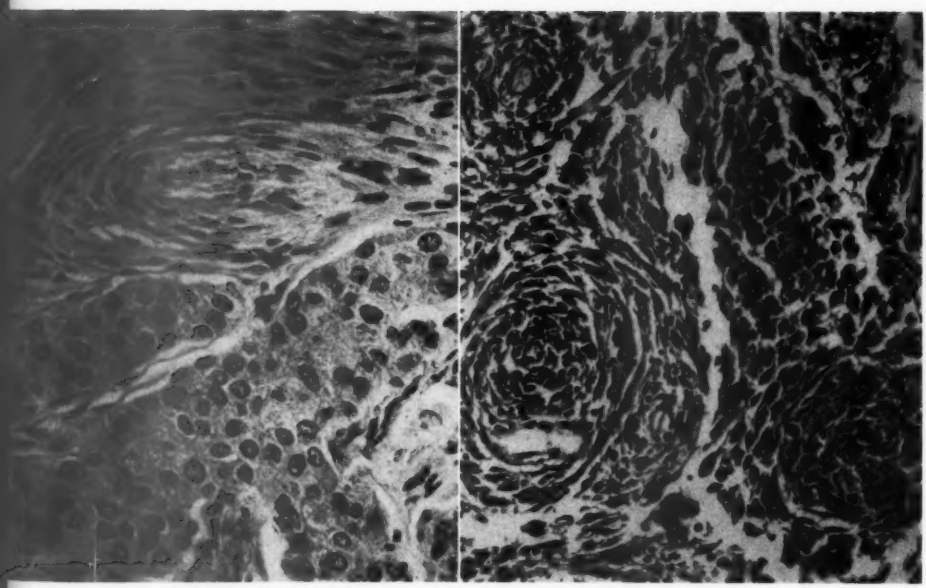

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BENIGN AND MALIGNANT CHORDOMAS
A Clinico-Anatomical Study of Twenty-Two Cases*

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It is convenient to divide chordomas into benign and malignant types. The benign lesions have been found only at necropsy except for the benign coccygeal chordoma included in this report, which was found by chance in a surgical specimen. The relative inaccessibility of the asymptomatic benign tumor accounts for this scarcity of case reports in comparison to the several hundred malignant chordomas that have been described in the literature.[1,2]

Benign Chordomas

A summary of four benign chordoma cases follows:

Case 1

A 68-year-old man was admitted to the University Hospital with hypertensive arteriosclerotic heart disease and prostatism. He died suddenly 5 days following a minor surgical operation. No symptoms or physical findings relative to the base of the brain, except for bilateral nerve deafness, were elicited. At necropsy the findings of arteriosclerotic heart disease were demonstrated. In addition, a section through the pituitary gland showed a mass of physaliferous cells outside the circular sinus in the sulcus between the anterior and posterior lobes (Fig. 1). Serial sections showed the chordoma cells outside the circular sinus throughout the thickness of the paraffin blocks.

Case 2

A 32-year-old woman died 24 hours after an osteoplastic craniotomy for a spongioblastoma polare of the right side of the brain stem and the right thalamus. A necropsy limited to the head showed the remainder of the glioma and also a benign chordoma which was loosely attached to the ventral surface of the pons. No attachment to the clivus was noted. Microscopically the chordoma was composed of large vacuolated cells with little intercellular mucin.

Case 3‡

A 61-year-old woman in an institution because of involutional psychosis died of coronary thrombosis. At necropsy the brain stem showed

* Received for publication, January 18, 1952.
† Now at the National Cancer Institute, Bethesda, Md.
‡ Case reported through the kindness of Dr. Konstantin Scharenberg.

a gray-white, gelatinous nodule, 0.8 cm. in diameter, which had a very loose attachment to the right anterior surface of the pons. No dural attachment was noted. Vacuolated and non-vacuolated cells made up the neoplasm and cords of cells were separated by intercellular mucin.

Case 4

A 44-year-old man had rectal symptoms referable to hemorrhoids. Through the sigmoidoscope a specimen for biopsy was obtained from a lesion on the anterior rectal wall, 11 cm. above the anus. This proved to be a carcinoid. Coccygectomy was done to facilitate removal of a segment of rectum. A routine section of the coccyx showed a benign chordoma arising in the first intercoccygeal disk and growing beneath the periosteum on the posterior surface of the coccyx (Figs. 2, 3, and 4). Serial sections of the coccyx showed the tumor growing along the surface of the disk on the right side of the coccyx and nearly surrounding it. It did not extend completely through the periosteum.

Discussion

Virchow[3] and Luschka[4] were first to describe the benign chordoma on Blumenbach's clivus. They interpreted it as a chondromatous neoplasm, and ecchondrosis physalifora spheno-occipitalis was used by Virchow and his followers to designate the lesion. Müller[5] and Ribbert[6] established the origin of this neoplasm from notochordal tissue and the name was changed later to ecchordosis physalifora spheno-occipitalis. Stewart and Burrow[1] reported 4 cases arising from Blumenbach's clivus.

With the demonstration of collections of histologically similar cells having the features of benign neoplasms at different levels along the original tract of the notochord from the pituitary region to the coccyx, it seems unnecessary to continue to use the cumbersome term ecchordosis physalifora and better to refer to the lesion as a benign chordoma, particularly when it occurs in adults. The term notochordal rest has some usefulness in designating collections of physaliferous cells in fetuses and young children which persist in the vertebral portion of the notochordal canal and which lie along the irregular branches of the original notochord. The latter can be referred to also as ectopic notochordal rests or chordal ectopia after Horwitz.[2]

The physaliferous cells of the notochord which give rise to the nucleus pulposus and which can be found in that structure until about the seventh year of life are referred to in this paper as nucleus pulposus cells.[7] Some workers have described these cells in later life in the

intervertebral disk and sacrum.[8,9] The acquired Schmorl's nodule and the posteriorly herniated nucleus pulposus have no special relation to the chordoma problem since these retrogressive lesions do not contain nucleus pulposus cells except in rare instances.[8] Eckert and Decker[10] failed to find nucleus pulposus cells in adult cadavers or in herniated intervertebral disks.

In spite of the limited number of case reports, a fairly high incidence of benign clival chordomas has been determined. Ribbert[11] found 10 cases in 500 necropsies or an incidence of 2 per cent. Stewart and Burrow[1] found 3 examples in 200 necropsies or a 1.5 per cent incidence. The incidence has not been determined for the pituitary region, the dens epistropheus, or the coccyx. From Schmorl's collection of spines Beadle[12] reported 7 cases of persistent notochordal cells which can be interpreted as benign chordomas. Six were in dorsal vertebrae and one was in the first lumbar vertebra.

The benign chordoma is an asymptomatic lesion. On Blumenbach's clivus the small, soft tumor is circumscribed and has not been shown to give pontine or bulbar symptoms. A thin pedicle attached through a defect in the dura to the underlying bone is found in most cases but was not observed in the cases reported here. The cells making up the neoplasm are quite uniform. They may or may not have vacuolated cytoplasm and the amount of intercellular mucin varies, but large pools of mucin often found in the malignant chordomas were not found in these 4 cases. Neoplasm size, invasiveness, mitotic figures, pleomorphism, excessive mucin formation, and other features of malignancy readily separated these benign neoplasms from the malignant cases. The similar location and cell type of the notochordal rests, nucleus pulposus cells, the benign chordoma, and the malignant chordoma indicate a close relationship of these four cellular configurations. Ribbert[13] and Congdon[14] have studied this problem experimentally and produced a lesion in rabbits by puncturing the nucleus pulposus which morphologically resembled a chordoma. True malignancy was not observed.

Malignant Chordomas

The malignant chordoma is considered a rare neoplasm and for this reason is a diagnostic problem. A general survey, however, of all primary supporting tissue neoplasms of the vertebral column seen in the Department of Pathology indicated that it formed a significant percentage of this group, particularly if neoplasms of the spinal cord and its meninges were excluded. A brief summary of each case follows.

Case 5

A 13-year-old boy was struck on the head by a stone 2 years before admission. Following this he had a stiff neck, with pains in head and neck. Five weeks before admission he developed nausea, vomiting, dizziness, and convulsions. Physical examination showed involvement of the left 11th and 12th cranial nerves. There was a scar on the occiput from the original injury. Roentgenologic examination showed a normal skull and cervical spine. A clinical diagnosis of posterior fossa tumor in the left cerebellar region was made. Death occurred during attempted operative removal. At necropsy, limited to the head, a tumor 3 cm. in diameter was situated beneath the left lobe of the cerebellum and anterior to the pons. It was firmly attached to the basilar meninges and extended from the foramen magnum to the posterior clinoid processes. It eroded the base of the skull at the foramen magnum and the inner portion of the petrous ridge on the left. The spinal accessory nerve was stretched over the tumor and the left vertebral artery lay in a groove in the tumor. Microscopically, the neoplasm was poorly differentiated. The cells in a few areas showed vacuolation of the cytoplasm and a slight amount of intercellular mucin (Fig. 5).

Case 6

A 40-year-old white female complained of severe pains in the left side of the head beginning 5 months before admission. Following this, she developed a staggering gait, blurring of vision, tinnitus, numbness of the left side of the face, weakness of the left arm and leg, difficulty in swallowing, and stiffness of the tongue. Physical examination showed a staggering gait, with cerebellar signs on the left and bilateral nystagmus on lateral gaze. There was left facial paresis and slight tactile loss in the distribution of the left 5th cranial nerve. There was absence of the left supra-orbital reflex, with neuroretinitis, and concentric contraction of the visual fields. A clinical diagnosis of a large left cerebellar tumor, possibly a left acoustic tumor, was made. At operation, on elevating the left cerebellar hemisphere, a tumor was seen pushing the 7th, 8th, 9th, 10th, and 11th cranial nerves outward. The capsule of the gelatinous granular neoplasm was incised and as much of the tumor removed as possible. Erosion of the basilar portion of the occipital bone was present. The patient was hospitalized for 2 years following the operation. About 1 year before her second admission she left the hospital. Severe headaches, projectile vomiting, weight loss, and difficulty with ambulation preceded the second admission. She died immediately following a partial surgical removal of a large

recurrent chordoma. At necropsy, the neoplasm covered the anterior surfaces of the pons and medulla oblongata, extending from the partially destroyed posterior clinoid processes to the lower margin of the medulla oblongata. Destruction of bone at the base of the skull and laterally of the petrous portions of the temple bones was present. Both cavernous sinuses were invaded. All cranial nerves excepting the first and second were surrounded by neoplasm. The microscopic structure of the chordoma was similar for both surgical specimens.

Case 7

A 16-year-old white female developed severe headaches which occurred daily about 3 years before admission. Vomiting and double vision developed about 3 months before admission. Physical examination showed papilledema, cerebellar signs, absent abdominal reflexes, horizontal nystagmus to the right and left, spastic tetraparesis with weakness more pronounced on the right, disturbance of posterior column function on the right, bilateral damage of spinal nerve roots in the uppermost cervical segment, and involvement of 11th and 12th cranial nerves. A myelogram showed obstruction at the inferior margin of the atlas. A clinical diagnosis of a lesion at the upper cervical cord and lower medulla oblongata was made. At operation a pale, gelatinous, granular, tumor mass was found anterior to the cervical cord and medulla. Severe arterial hemorrhage was encountered and the patient died during the operative procedure. No necropsy was performed. The microscopic sections of the surgical specimen showed masses of vacuolated cells in a mucinous matrix.

Case 8

A 17-year-old white female complained of headache and blurred vision for 4 months prior to admission. Three weeks before admission she developed nausea and vomiting. Tinnitus in the right ear and staggering gait as well as hoarseness and vocal weakness developed about 2 weeks prior to admission. There was moderate weight loss, with general weakness and fatigue. Physical examination showed bilateral papilledema with questionable abnormal downward convergence and questionable proptosis of the left eye. Hoarseness, diminished gag reflex, and difficulty in swallowing were present. The tongue showed atrophy on the left as well as deviation to the left. A positive Romberg test and ataxic gait were present. Roentgenologic study showed a space-occupying lesion in the region of the pons displacing the third ventricle upward and the aqueduct of Sylvius backward. Visual field studies showed enlargement of the blind spot on the left and a right

homonymous hemianopsia. At operation a large tumor lay on the anterior and left lateral aspects of the pons. Decompression was carried out and the patient died the following day. Necropsy was not performed. Microscopic examination of the surgical specimen showed some cytoplasmic vacuoles but more striking nuclear vacuoles. A moderate amount of intercellular mucin was present in a few areas (Figs. 6 and 7).

*Case 9**

A 52-year-old white female fell from a chair about 2 years before admission. Severe head pain and stiffness of the neck followed. Prior to death she developed difficulty in swallowing, paresthesia of the hands, and weakness of the upper and lower extremities. Physical examination in the year prior to death showed a tender, cherry-sized thickening over the second cervical vertebra. Spastic tetraparesis was present and involvement of the 11th and 12th cranial nerves. Throughout her 3-year illness the patient was thought to have cervical Pott's disease. At necropsy a neoplasm was found to extend from the medulla oblongata through the foramen magnum and to involve the first and second cervical vertebrae extensively. The neoplasm grew within the spinal dura mater. Microscopically, the large vacuolated neoplastic cells lay in pools of mucin.

Case 10

A 31-year-old male had symptoms about 8 or 10 years before the first excision. These consisted of a nasalized voice and nasal obstruction with a gradually developing mass in the throat. In 1925, an intra-oral excision was performed followed by local application of radium. For about 9 years he was symptom free. A second excision was performed in 1935 and a recurrence appeared shortly afterwards. In 1937 a nasopharyngeal cyst was removed with some relief of symptoms. The third and final excision performed in 1940 was not considered complete because invasion of the body of the atlas was thought to be present. At the time of the final excision the neoplasm consisted of an ovoid mass, 2 cm. in diameter, in the midline, elevating the posterior pharyngeal wall. It pressed the soft palate forward. The mucous membrane was not involved. Roentgenograms showed irregularity of the anterior surface of the body of the atlas. Repeated check-ups for 4 years showed no evidence of recurrence and the patient died 5 years following the final excision. Death was attributed to cardiac failure and Bright's disease by the patient's home physician. Speci-

* Published through the kindness of Drs. Jacob Erdheim, deceased, and C. V. Weller. The necropsy was performed at the Wiener Allgemeines Krankenhaus in 1925.

mens from two of the excisions (1925, 1940) showed vacuolated and non-vacuolated cells in a mucinous matrix. There was no necropsy. This is the only instance in the entire series of malignant cases in which a clinical cure may have been obtained.

Case 11

A 50-year-old white male complained of attacks of pain in the back, radiating to the right arm, weakness of the right arm and leg, incontinence of urine and feces, and loss of vocal strength. These symptoms had a gradual onset over a period of 1 year before admission. Sensory loss from the upper thorax down and progressive respiratory difficulty characterized the period immediately before admission. Physical examination showed respiratory distress. He talked in a whisper. The sensory level corresponded to the cervicotrigeminal junction on the left and to the third cervical segment on the right. Papilledema, lingual paralysis, inability to raise his head, flaccid paralysis of the lower extremities, and absence of deep tendon reflexes were present. Clinical diagnosis was that of a space-occupying lesion from the first to the third cervical vertebra. The patient died 2 days following partial surgical removal. At necropsy, after removal of the vertebral laminae, a subperiosteal tumor was found extending from C 1 to C 5 on the left posterolateral wall of the vertebral bodies. From C 2 to C 4 a tumor mass narrowed the lumen of the spinal canal by about two-thirds. The prosector thought that the neoplasm arose from the left posterolateral aspect of the intervertebral disk between C 1 and C 2. Microscopically, the neoplasm was composed of vacuolated and non-vacuolated chordoma cells. Some mucin formation was present and the cells tended to be poorly differentiated, with many hyperchromatic nuclei.

Case 12

About 1 year before admission an 18-year-old female noted onset of pains in the chest and back. Gradually paralysis of the legs developed. Physical examination revealed irregular pupils, nystagmus, left facial weakness, increased deep tendon reflexes, bilateral abortive ankle clonus, absent vibratory sense in the lower extremities, and semiflaccid spastic paralysis of the lower extremities. Roentgenograms of the dorsal and lumbosacral vertebrae were normal. A clinical diagnosis of spinal cord tumor at C 8 was made. At operation an extradural tumor 4 cm. long and 2 cm. wide was found. The seventh cervical nerve was stretched over the tumor. After removal, the posterior surface of the body of the seventh cervical vertebra was found to be roughened and the surgeon noticed that the tumor did not come from

an intervertebral disk. Extension of the tumor through the seventh intervertebral foramen was noted. Death occurred 13 months following the surgical procedure. No necropsy was performed. Before death, roentgenograms of the chest showed a soft tissue tumor mass in the left apical region. It was sharply circumscribed and extended into the thoracic inlet for about 3 cm. from the vertebral border. The trachea was displaced to the right. There was destruction of the bodies of the first and second thoracic vertebrae and the first thoracic body had slipped downward and over the second. Microscopically the tumor consisted of vacuolated chordoma cells invading dense connective tissue. There was very little mucinous matrix. Nearly every cell was vacuolated.

Case 13

A 62-year-old male noted postural low back pain which was intermittent at first but became constant, with radiation down both legs to the feet about 6 months before admission. The pain was associated with increasing constipation and pencil-sized stools. Physical examination showed a palpable descending colon. There was hypo-esthesia, more marked on the right, in the lateral sacral regions corresponding to the fourth sacral nerves. Diminished Achilles reflex and decreased vibratory sense in the lower extremities were more marked on the right. There was tenderness over the lumbo-sacral region. Roentgenograms showed gross irregularity, predominantly on the left, of the dorsal portion of the first lumbar vertebral body and pedicle. A myelogram showed complete block at the level of the first lumbar vertebra. The clinical diagnosis was a lesion at the conus terminalis. Chordoma was considered, as was neoplasm of the colon. At the first operation a tumor lying anterior to the posterior spinal ligament was described as being the size of a large olive and was thought to be coming from the intervertebral disk between the first and second lumbar vertebrae. It had produced angulation of the cord by backward pressure. Complete excision was thought to have been obtained and tumor substance in the vertebral body was cauterized. Figure 8 shows the microscopic picture. About 1 month following operation an erythema dose (650 r. to an 8 by 10 cm. field) of x-ray irradiation was given the tumor site along the spine. Three months later a similar dose was given to the same field. The patient was reasonably well for about 2½ years following these procedures. He then developed severe pain in the back and received a third x-ray treatment of 600 r. to a 20 by 15 cm. field over the original tumor area. His pain became much worse following the x-ray therapy and a second operation was performed. The recurrent chordoma invaded the lower lumbar vertebrae and extended into

the paravertebral muscles. A large amount of tumor was excised in order to decompress the cauda equina and upper conus terminalis. The second surgical specimen was similar to the first. Following this, the patient experienced little benefit and was admitted to a series of hospitals elsewhere. It is believed that he died a few months later because of the neoplasm.

Case 14

A 47-year-old white male had had his coccyx removed 11 years prior to admission for an undetermined condition. Eight years before admission he had had an injury to the spine. His present illness had its onset 3 years before admission with pain in the back, the right hip and leg. There was also a weight loss of 45 lbs. and increasing constipation. Physical examination revealed pain on thumping the lower spine, a list to the right on standing, absent knee jerks, sluggish Achilles reflexes, and diminished vibratory sense in the lower extremities. Roentgenograms showed a destructive process of the posterior and left side of the third lumbar vertebral body. A left psoas bulge was present and widening of the neural canal at this point. The clinical diagnosis was that of spinal cord tumor at the second and third lumbar vertebrae. At operation a bluish gray, gelatinous tumor was found extradurally on the left lateral aspect of the spinal cord, extending anteriorly. It invaded the body of the third lumbar vertebra. After the operation an erythema dose of deep x-ray therapy was given over the operative site. Following these procedures the patient remained bedridden because of severe pain. About 10 months later a bilateral anterolateral chordotomy was performed at the level of the seventh cervical spine. This procedure was unsuccessful and intractable pain continued. A second chordotomy was performed about 1 year later. A large tumor mass developed over the lower lumbar spine and the patient died about 1 year and 5 months following the second chordotomy. Necropsy was not performed. Microscopically, cords of chordoma cells were present lying in pools of mucin.

Case 15

A 57-year-old man gave a history of having injured his sacrum about 36 years prior to admission. About 2 years before admission he noted onset of constipation with development of ribbon stools. A mass developed over the sacrum followed by sciatic pain. Fecal incontinence and urinary frequency developed about 2 weeks prior to admission. Physical examination revealed a hard mass over the lower sacrum, severe sciatic pain on palpation, careful gait, left leg held semiflexed, absent knee jerks, sensory loss over the sacrum, and relaxation of the

anal sphincter. Ankle jerks were diminished. Saddle anesthesia with hypo-esthesia over the genitalia were present. A retropubic mass could be palpated and also a mass filling the hollow of the sacrum was found on rectal examination. Roentgenograms revealed a destructive lesion arising from the fourth and fifth sacral segments, more on the left than the right. The clinical diagnosis was that of a sacral tumor involving the third and fourth sacral nerves on the left and the fourth and fifth sacral nerves on the right. At operation, the sacrum, coccyx, posterior tumor mass and the tumor mass filling the pelvis were excised with great difficulty. Neoplasm extending upward into the spinal canal was also excised as were involved laminae. About 7 weeks following operation the patient died, probably of spinal meningitis. Necropsy was not performed. Microscopically, the neoplasm consisted of cords and strands of chordoma cells in a mucinous matrix. Some contained large vacuoles. Many of the nuclei were hyperchromatic.

Case 16

A 65-year-old white male had onset of pain in the back about 4 years before admission. The pain radiated to the right leg. Constipation and ribbon stools gradually developed. Physical examination revealed an orange-sized mass in the hollow of the sacrum which was tender to palpation. Vibratory sense was diminished at the ankles. Spinal puncture showed a complete block. Roentgen examination revealed widened space between the sigmoid colon and the sacrum. A calcareous shadow was present along the posterior surface of the lumbosacral articulation. The clinical diagnosis was chordoma or neurofibroma. At operation a 10 by 10 by 6 cm. tumor, attached to the upper anterior surface of the sacrum and occluding the sigmoid colon by pressure, was removed. It was thought at the time of operation that complete removal was not obtained, as there was infiltration in the region of the sigmoid colon. A recurrence developed and the patient died of neoplasm about 3 years later. Necropsy was not performed. Microscopically the tumor was composed of vacuolated chordoma cells with a mucinous matrix.

Case 17

A 53-year-old white female noted pain in the lower back with radiation in the sciatic areas of both thighs, which had had its onset about 1 year before admission. There were numbness and paresthesia over the buttocks and in the lower extremities. She had been confined to bed by pain for 8 months prior to admission. Bowel and bladder incontinence was present. Physical examination showed pain on pressure

over the coccyx. There was no rectal mass. Saddle anesthesia with extension to right buttock, weakness of both legs, and hyperactive knee jerks were present. Absent ankle jerks and a right Babinski sign were noted. Roentgenograms showed destruction of the sacrum below the first sacral segment with apparent expansion of the sacral body. The clinical diagnoses were those of conus terminalis lesion and chordoma. A biopsy was performed, but no treatment was instituted. Two years later roentgenograms showed destruction of the entire sacrum with additional destruction of the last lumbar vertebra and the medial portions of the ilia. Prior to death the patient developed a large mass in the sacral region. Microscopically, the biopsy showed bulky fragments of vacuolated chordoma cells.

Case 18

A 53-year-old white male had his sacrum injured by a blow 1 year prior to developing a lump on the sacrum. In 2 years the lump grew to the size of an egg. No other symptoms were recorded. Operative removal was performed but recurrence developed and in 5 years an orange-sized mass could be palpated in the hollow of the sacrum. It presented also beneath the anal skin. A second excision was performed. In addition, the patient received three x-ray treatments of 200 r. each over the sacrum and coccyx. Eleven years later a third excision was performed. The baseball-sized tumor mass over the lower sacrum involved gluteal muscles on either side. Three years later a fourth excision was carried out of a tumor measuring 6 by 8 cm., which covered the remaining portion of the sacrum and extended into the sacral foramina. The patient died of bronchopneumonia following operation. At necropsy, masses of neoplasm cells were found microscopically in the operative area. The several surgical specimens showed no essential variation and consisted of vacuolated chordoma cells in a mucinous matrix.

Case 19

A 76-year-old female injured her back 4 or 5 years prior to admission, while lifting a patient. She had onset of pain in the sacrum about 2 years before admission. This was exacerbated by straining at stool. Some constipation was present. Physical examination showed a sausage-shaped mass lying in the hollow of the sacrum, which could be felt on rectal palpation. Roentgenologic examination showed anterior displacement of the rectosigmoid junction, with non-visualization of the lower end of the sacrum and coccyx. The clinical diagnosis was that of a sacral tumor. At operation the eroded sacrum and coccyx and tumor were removed en bloc. The moderately well encapsulated tumor

mass weighed 105 gm. and measured 7 by 8 by 4.5 cm. (Fig. 11). Microscopically, it showed a variable pattern but some areas had vacuolated cells in a mucinous matrix (Figs. 9, 10, 12, and 13). Careful study of the margins of the specimen showed that the neoplasm extended to the line of excision in at least one area. The patient continued to have severe pain following operation and was bedridden most of the time. No recurrent neoplasm could be palpated on two physical examinations. She died about 1 year following the surgical excision. Necropsy was not performed.

Case 20

A 68-year-old white male was admitted because of dysuria and severe pain in the back. Physical examination showed a grape-fruit sized mass attached to the left portion of the sacrum. On rectal examination there was a large retrorectal mass involving the left side of the sacrum. Roentgenograms showed a destructive lesion involving nearly all of the sacrum and expanding its cortex. The cortex was broken through in numerous places. The clinical diagnosis was sacral chordoma. At operation the large tumor mass was determined to be inoperable and biopsy was performed. Microscopically, the neoplasm consisted of vacuolated and non-vacuolated chordoma cells with some mucinous matrix. Infiltration of bone was present. The patient was discharged and a follow-up report several months later indicated that the patient was having great pain, and could feel the mass in the sacral area.

Case 21

A 26-year-old female had a tumor removed from the sacral area, which had been diagnosed as a malignant cystadenoma. Eight years later a large encapsulated tumor in the same region was removed and on microscopic examination showed chordoma cells in a mucinous matrix, with moderate nuclear pleomorphism and hyperchromatism. Later history was not obtained.

Case 22

A 59-year-old male had noted a tumor over the sacrum and coccyx for 7 years. This became tender and produced a throbbing pain in the sacral area. He had had an operation of unknown nature on the rectum 2 years before admission. Physical examination showed a semifluctuant, orange-sized mass attached to the coccyx. It was tender and extended to the posterior margin of the anus. Neurologic findings were not noted. Roentgenologic examination showed complete destruction of the coccyx and invasion of the terminal segments of the sacrum.

Clinical diagnosis was sarcoma of the coccyx. The neoplasm was excised and the patient received a single dose of 650 r. over the operative site. Four years later he had a large recurrent neoplasm measuring 12 by 12 by 5 cm., occupying the lower two-thirds of the sacrum and the space between the gluteal muscles. Neoplasm could be felt on rectal examination. Roentgenologic examination at this time showed destruction of the sacrum extending to the third sacral segment. In the year prior to death he received deep x-ray therapy consisting of 2000 r. to one sacral port and 1800 r. to two anterior ports over the inguinal regions. Following this there was relief of pain for 2 or 3 months but no change in the size of the tumor mass. Subsequently 1800 r. to two posterolateral ports cross firing the base of the tumor was given without noticeable effect. Necropsy was not performed.

Discussion

The 18 cases reported here illustrate nearly all of the clinical and pathologic features associated with malignant chordomas in the several anatomical locations in which the tumors arise. Tables I and II summarize pertinent clinical and anatomical data.

Table I

Location, Age, Sex, and Duration of Malignant Chordoma Cases

Case no.	Age	Sex	Location	Approximate duration of illness
5	13	M	Blumenbach's clivus	2 yrs.
6	40	F	Blumenbach's clivus	4 yrs.
7	16	F	Blumenbach's clivus	3½ yrs.
8	17	F	Blumenbach's clivus	4 mos.
9	52	F	Cervical vertebrae 1 and 2	3 yrs.
10	31	M	Cervical vertebra 1 and nasopharynx	25 yrs.
11	50	M	Cervical vertebrae 1 and 2	1 yr.
12	18	F	Lower cervical and uppermost thoracic vertebrae	2 yrs.
13	62	M	Lumbar vertebrae 1 and 2	5 yrs.
14	47	M	Lumbar vertebra 3	6 yrs.
15	57	M	Sacral segments 4 and 5	2 yrs.
16	65	M	Upper sacrum	7 yrs.
17	53	F	Sacrum	7 yrs.
18	53	M	Lower end of sacrum	19 yrs.
19	76	F	Lower end of sacrum and coccyx	3 yrs.
20	68	M	Sacrum	Still living after 3½ yrs.
21	26	F	Sacrum	At least 8 yrs., no follow-up
22	59	M	Coccyx	10 yrs.

TABLE II

Therapy Used in Malignant Chordoma Cases

Case no.	Surgical excisions and explorations	X-ray and radium therapy
5	Death during suboccipital craniectomy, 1925	None
6	(a) Suboccipital craniectomy, 1930 (b) Death following suboccipital craniectomy for recurrent chordoma, 1933	None
7	Death during suboccipital craniectomy and cervical laminectomy, 1939	None
8	Death 1 day following surgical decompression	None
9	None	None(?)
10	(a) Intra-oral excision, 1925 (c) Intra-oral excision, 1935 (d) Incision, nasopharyngeal cyst, 1937 (e) Intra-oral excision, 1940; not considered complete but patient apparently cured	(b) 50 mg. of radium in nasopharynx for 12 hrs.; 2 mos. later 50 mg. of radium in nasopharynx for 14 hrs.; 1925
11	Death following cervical laminectomy, 1942	None
12	Death 3 mos. following cervical laminectomy, 1930	None
13	(a) Lumbar laminectomy, 1935 (c) Death 10 mos. following lumbar laminectomy, 1938	(b) Erythema dose over tumor site along spine, 8 x 12 cm. field, 650 r., following operation; repeated 3 mos. later (d) 20 x 15 cm. field, 600 r., single dose, 1938, following operation
14	(a) Lumbar laminectomy, 1934; death 3 yrs. later (c) Chordotomy for pain, 1935 (d) Chordotomy for pain, 1936	(b) Single erythema dose of x-ray irradiation over operative site, 1935
15	Death from meningitis 1 mo. following surgical removal of sacral chordoma, 1934	None
16	(a) Enucleation of sacral chordoma, 1939 Death 3 yrs. later	(b) X-ray therapy elsewhere, 1940(?)
17	(a) Biopsy, 1942, of sacral chordoma; death 6 yrs. later (b) Bilateral cervical chordotomy for pain	None
18	(a) Excision of sacral chordoma elsewhere, 1925 (b) Excision, 1930 (d) Excision, 1941 (e) Excision, 1944; death 1 mo. later	(c) Following operation 200 r. to 15 x 15 cm. field over sacrum, 6/9/30; 200 r. to 15 x 15 cm. field over coccyx, 6/10/30; 200 r. to 15 x 15 cm. field over coccyx, 6/11/30
19	Excision, 1949; death about 1 yr. later	None
20	Biopsy, 1950	None
21	(a) Excision of sacral chordoma about 1932 (b) Excision, 1941	Not known
22	(a) Excision of sacral chordoma, 1935; death 5 yrs. later	(b) Single dose of 650 r. over operative site, 10 x 12 cm. field, 1935 (c) 1939, three ports: two anterior, one posterior; 2000 r. to sacral port, 1800 r. to anterior ports over inguinal regions (d) 1940, 1800 r. to two posterolateral ports, cross firing the base of the tumor

Except for the cases of Koritzky[15] and Rubaschow[16] involving the maxillary and mandibular alveolar ridges, and the more plausible case of Alezais and Peyron[17] in the left occiput outside of the skull, all chordomas have been found at the base of the skull or along the vertebral column. In this series 4 arose from Blumenbach's clivus; 3 were upper cervical including the nasopharyngeal chordoma; 1 was low cervical or upper thoracic; 2 arose from the lumbar region; 7 from the sacrum; and 1 from the coccyx. The dorsal spine is not represented definitely in this group of cases but origin in the dorsal spine has been reported.[18]

Ten of the patients were males and 8 were females. The ages at onset varied from the second decade to the eighth. The disease has been seen in the fetus[19] and in young children.[20]

The duration of the illness varied from 4 months to 25 years depending primarily on the location and secondarily on the treatment. In general, tumors of the base of the skull and cervical region cause death several years sooner than chordomas involving the lumbar, sacral, and coccygeal regions. The more often the tumor can be partially excised, the longer the life of the patient. Survivals of several years without surgical treatment were seen in cases 9, 17, and 20, indicating the slow growth of the neoplasm. This is in marked contrast to the brief course of 4 months of case 8, which arose from Blumenbach's clivus.

The prognosis of malignant chordoma is hopeless with the possible exception of such rare cases as case 10, a nasopharyngeal tumor, which is considered as demonstrating a possible cure. The inability to remove small lesions completely because of location, as in the lumbar region in case 13, or the failure of the surgeon to do more than enucleate a circumscribed accessible mass, as in cases 18 and 19, reduces the probability of effecting a cure. It is doubtful if clival and cervical chordomas which involve the central nervous system can be cured by present methods. The more radical surgical approaches advocated by Mixter and Mixter[21] and Coley[22] are definitely indicated in sacrococcygeal chordomas.

The treatment, other than surgical removal, has been x-ray therapy and radium application. Limited x-ray therapy was given to several of the patients but only case 22 involving the coccyx received adequate dosage and pain decreased for a few months without change in size of the neoplasm. Radium was applied to the nasopharyngeal area in case 10 after the first excision of the tumor.

Lack of radiosensitivity has been the experience of most x-ray thera-

pists with this tumor. Recently Wood and Himadi[23] indicated some usefulness for x-ray therapy in a large series of cases.

The clinical history, physical findings, and course of the illness are all related closely to the gross pathologic aspects of the tumor. Pain was the most prominent feature of the disease in these patients and was present in most at the outset. The invasion of bone, central nervous system, and nerves accounts for this finding. Special signs and symptoms related to the region were an important part in the clinical picture with intracranial and cervical chordomas. The nasopharyngeal case presented an otolaryngologic problem.

Case 12 showed an intrathoracic mass but it was not associated with special symptoms. The lumbar and sacral chordomas presented the findings and symptomatology of lesions of the conus terminalis and cauda equina. An additional problem was seen in the sacrococcygeal cases, with obstruction of the sigmoid colon and rectum simulating intraluminal tumors of these organs. Palpation of these masses through the rectal wall was of diagnostic value. Prior to death, an externally visible tumor mass developed with several of the lumbar, sacral, and coccygeal chordomas.

Metastases have been described in lymph nodes, liver, and other organs as a late manifestation of chordomas,[24,25] but none were found in these patients upon only 5 of whom were necropsies performed.

Grossly, the chordoma is a gelatinous gray-white tumor growing in alveolar masses (Figs. 11 and 12). Hemorrhage and necrosis in the tumor are common. Confusion with mucin-forming adenocarcinoma, chondrosarcoma, and myxoma has been a diagnostic problem in gross interpretation.

Microscopic diagnosis in all of these cases depended in the final analysis upon finding tumor cells with one or more cytoplasmic vacuoles lying in a mucinous matrix. Most of the variants described by Alezais and Peyron[17,26] were illustrated in this series.

Etiologic factors and the details of the histogenesis remain obscure. Some workers have thought that trauma plays an etiologic rôle because it is often referred to in case histories and because of the experimental work of Ribbert mentioned previously.[13,26] The rôle of trauma is not convincing in the cases reported here.

Origin of the malignant chordoma from either nucleus pulposus cells of the intervertebral disk, from benign chordomas, and from notochordal rests has been considered, but detailed proof of the source of the neoplasm has not been given. The neoplasms, in cases such as those presented here, are usually too large at the time of operation or necropsy to be of much help in studying histogenesis. Case 13 is a

possible exception since the surgeon described it as an olive-sized tumor coming from an intervertebral disk in the lumbar spine. If all or some malignant chordomas arise in benign neoplasms, the problem still remains whether the benign lesions come from nucleus pulposus cells or from notochordal rests. In general, the opinion about cell rests in recent years has been against the idea that they have some special propensity for undergoing neoplastic transformation in contrast to normally located cells.[27]

Case 4 of the benign chordoma series is of great value since the coccyx was sectioned serially and the neoplasm was seen to come out of the intersegmental disk. The tissue of the disk that would correspond to a nucleus pulposus showed rests of nucleus cells which were partly calcified. These 2 cases lend slight support to the idea that some chordomas originate from cells of a nucleus pulposus.

Resolution of the problem of histogenesis may be possible by the experimental approach.[14]

Conclusions

Four cases of benign and 18 of malignant chordoma have been reported. One of the benign chordomas was discovered in a surgical specimen of the coccyx.

No symptoms or clinical findings were attributable to the benign chordomas.

One of the 18 patients with malignant chordoma is still alive with neoplasm. One had no follow-up. The remaining 16 are all dead; one nasopharyngeal case may have been cured by repeated excisions and radium applications.

In 2 cases, one malignant and one benign, there was suggestive evidence that the neoplasm arose from nucleus pulposus cells of the intervertebral disk and from an intercoccygeal disk.

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DESCRIPTION OF PLATES

PLATE 120

FIG. 1. Case 1. Mass of physaliferous cells lying next to the circular sinus of the pituitary gland. Hematoxylin and eosin stain. × 250.

FIG. 2. Case 4. Partially calcified nests of physaliferous cells in the intercoccygeal disk. Hematoxylin and eosin stain. × 200.

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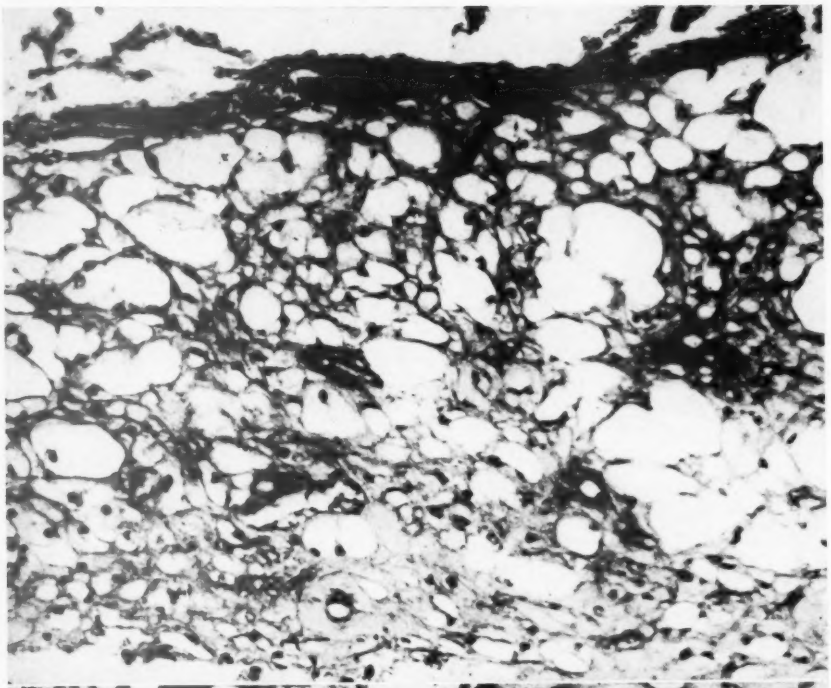

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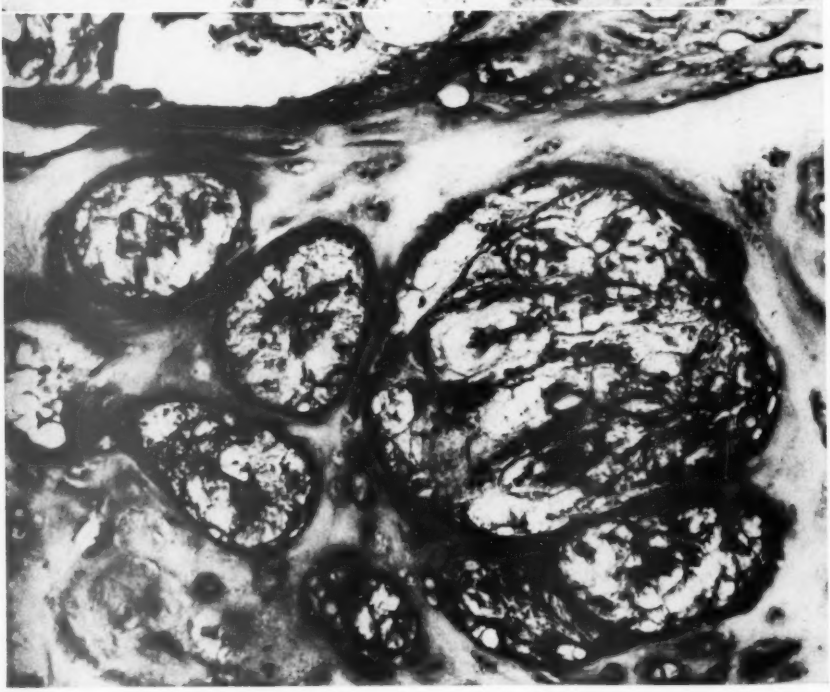

Congdon Benign and Malignant Chordomas

PLATE 121

FIG. 3. Case 4. Large nests of physaliferous cells on the surface of the first intercoccygeal disk. Hematoxylin and eosin stain. × 75.

FIG. 4. Case 4. Main tumor mass growing in dense connective tissue adjacent to the coccyx. Hematoxylin and eosin stain. × 65.

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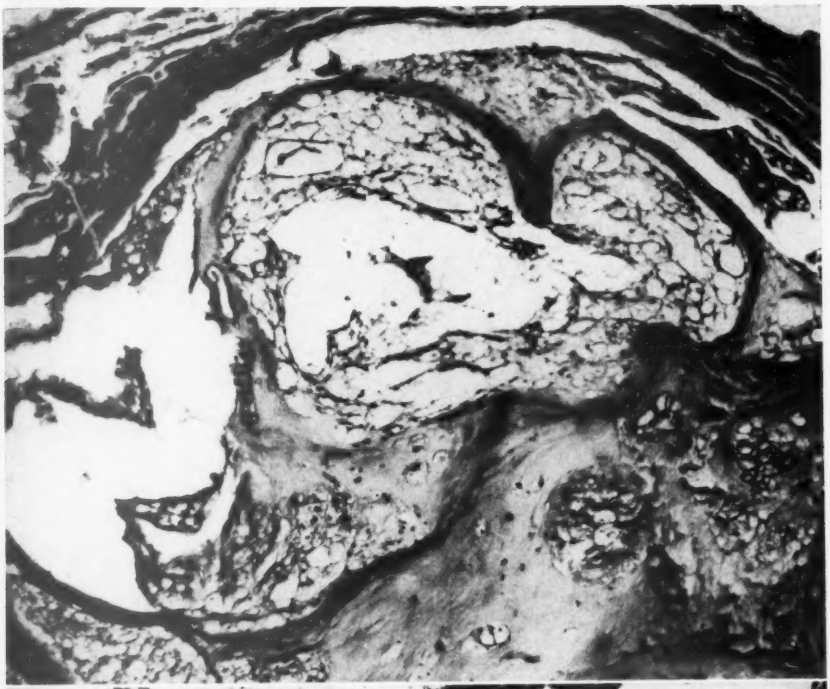

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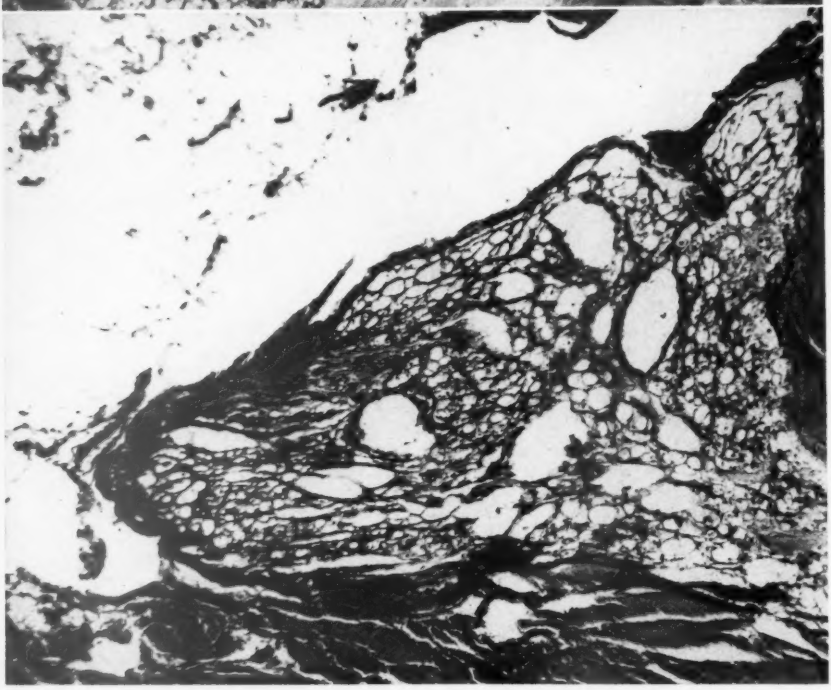
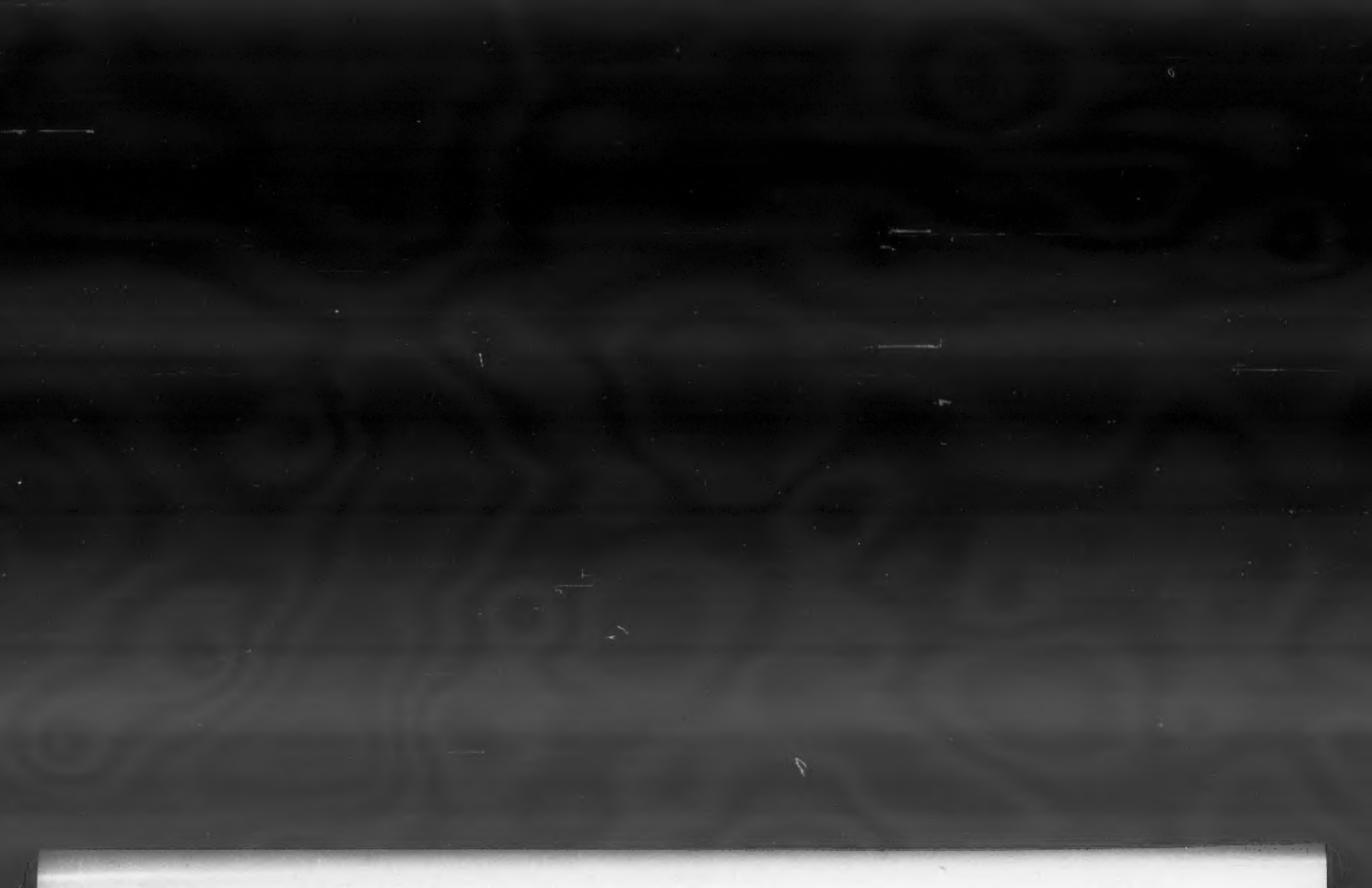


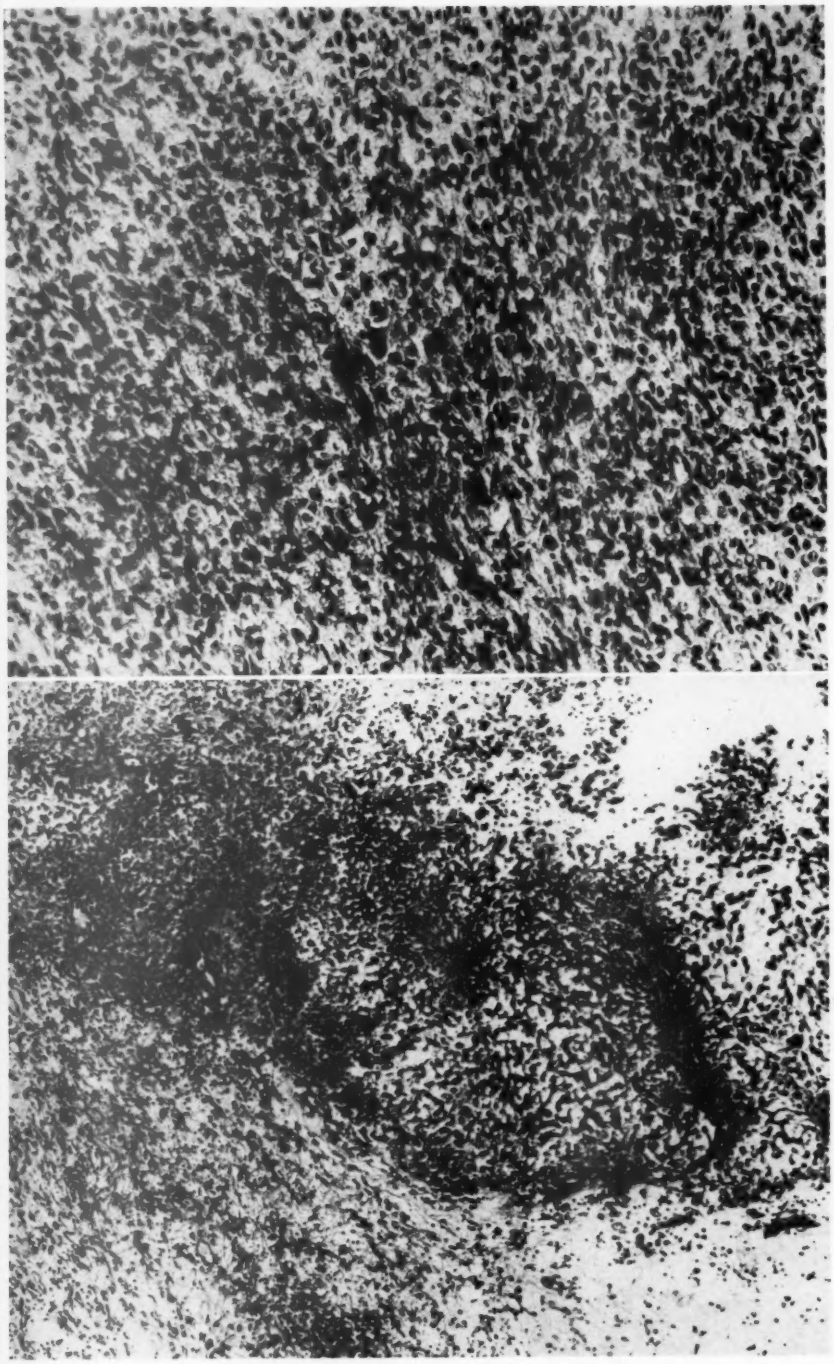
Congdon Benign and Malignant Chordomas

PLATE 122

FIG. 5. Case 5. Poorly differentiated chordoma of the clivus. The sarcomatous appearance is evident. Hematoxylin and eosin stain. × 250.

FIG. 6. Case 8. Mass of chordoma cells. Cords of cells are separated by a mucinous matrix. Hematoxylin and eosin stain. × 80.





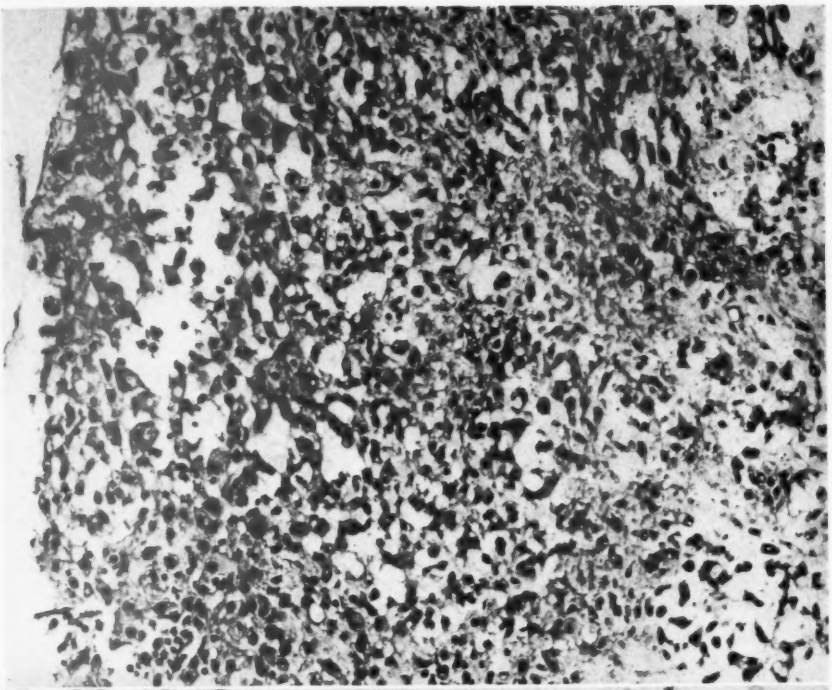
Congdon Benign and Malignant Chordomas

PLATE 123

FIG. 7. Higher power view from case 8 showing cells with vacuolated cytoplasm. Solitary vacuoles are present in the nuclei of many cells. Hematoxylin and eosin stain. × 200.

FIG. 8. Case 13. Cords of neoplasm cells in a mucinous matrix. Some show cytoplasmic vacuoles. Hematoxylin and eosin stain. × 250.

7



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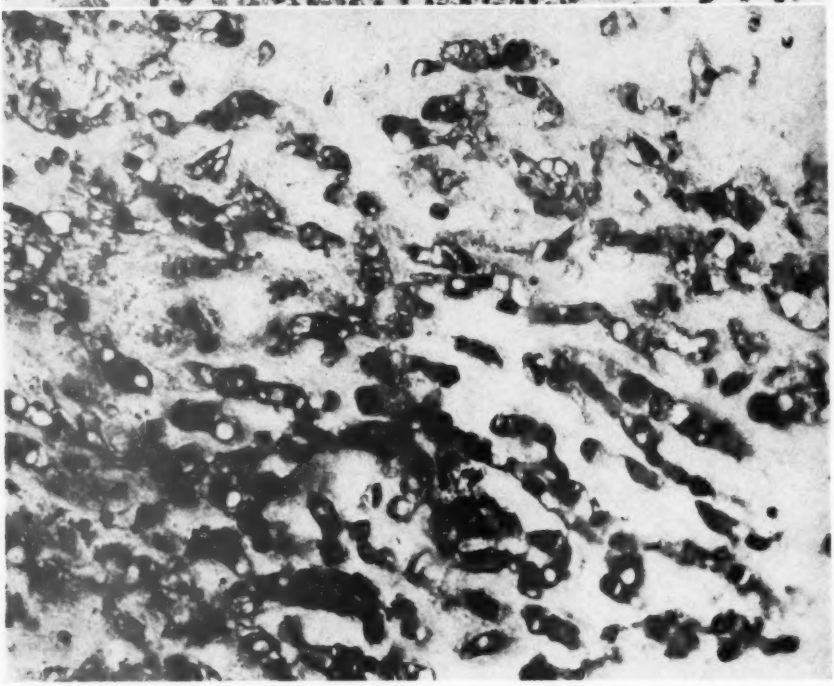
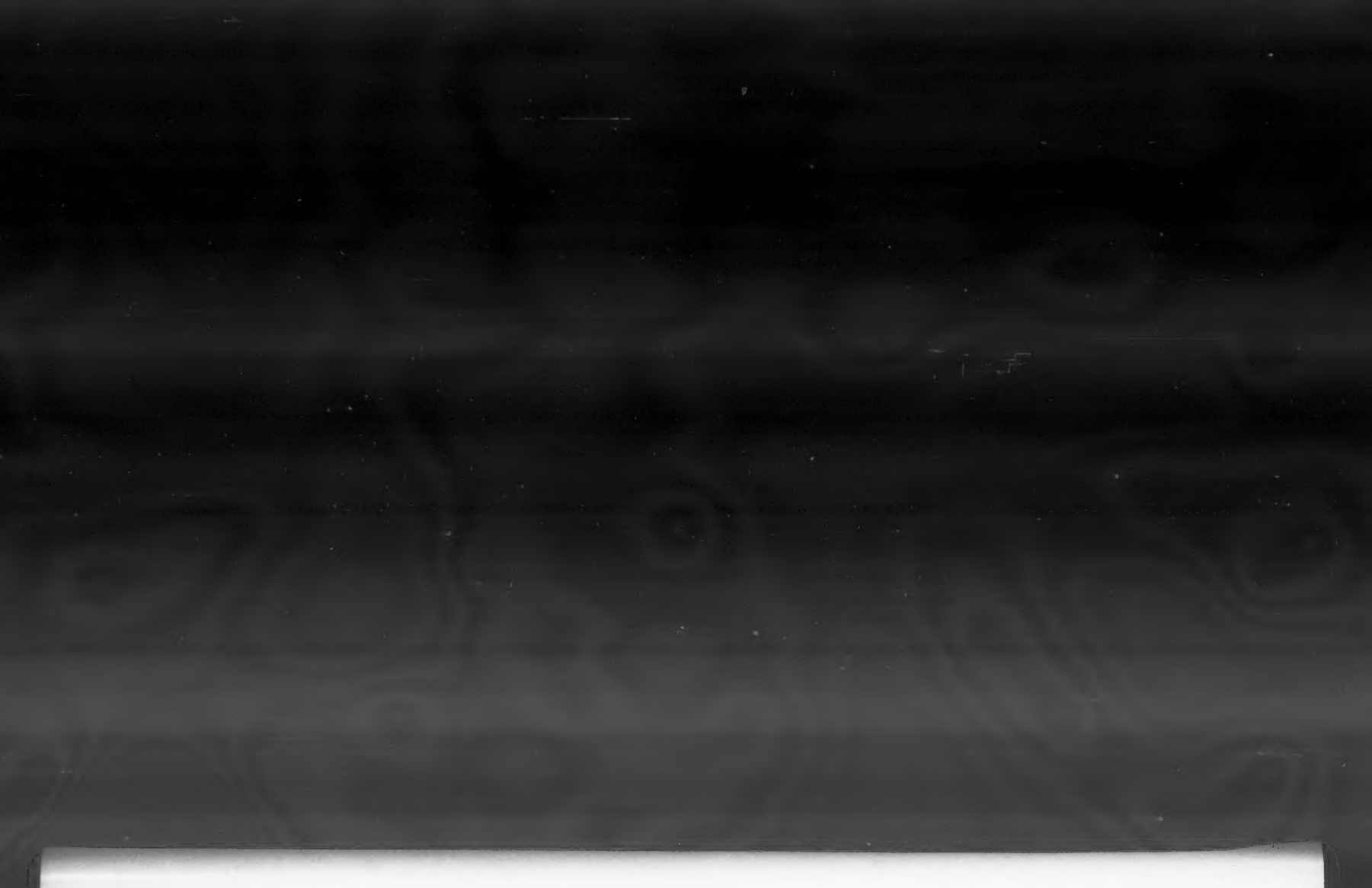


Congdon Benign and Malignant Chordomas

PLATE 124

FIG. 9. Case 19. Area of vacuolated cells from the edge of the main tumor mass. Hematoxylin and eosin stain. × 250.

FIG. 10. Another field from the same section as Figure 9, in which the mucinous matrix is dense, giving the tumor a cartilage-like appearance. Hematoxylin and eosin stain. × 200.



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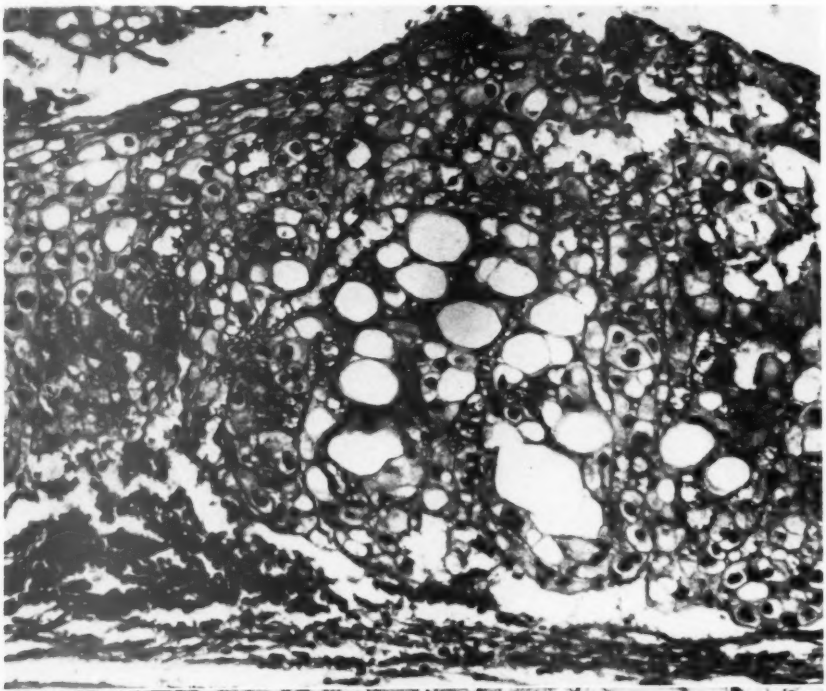

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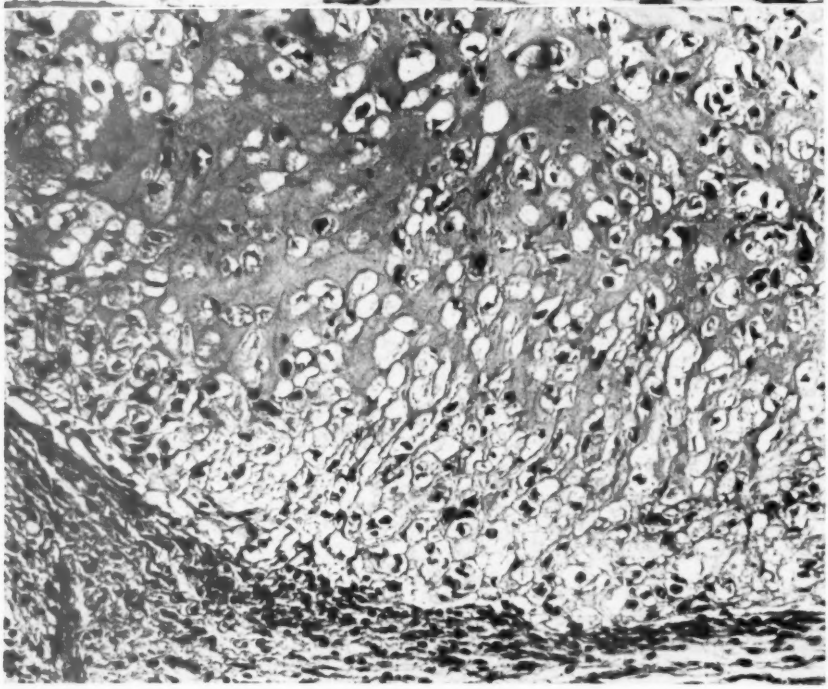


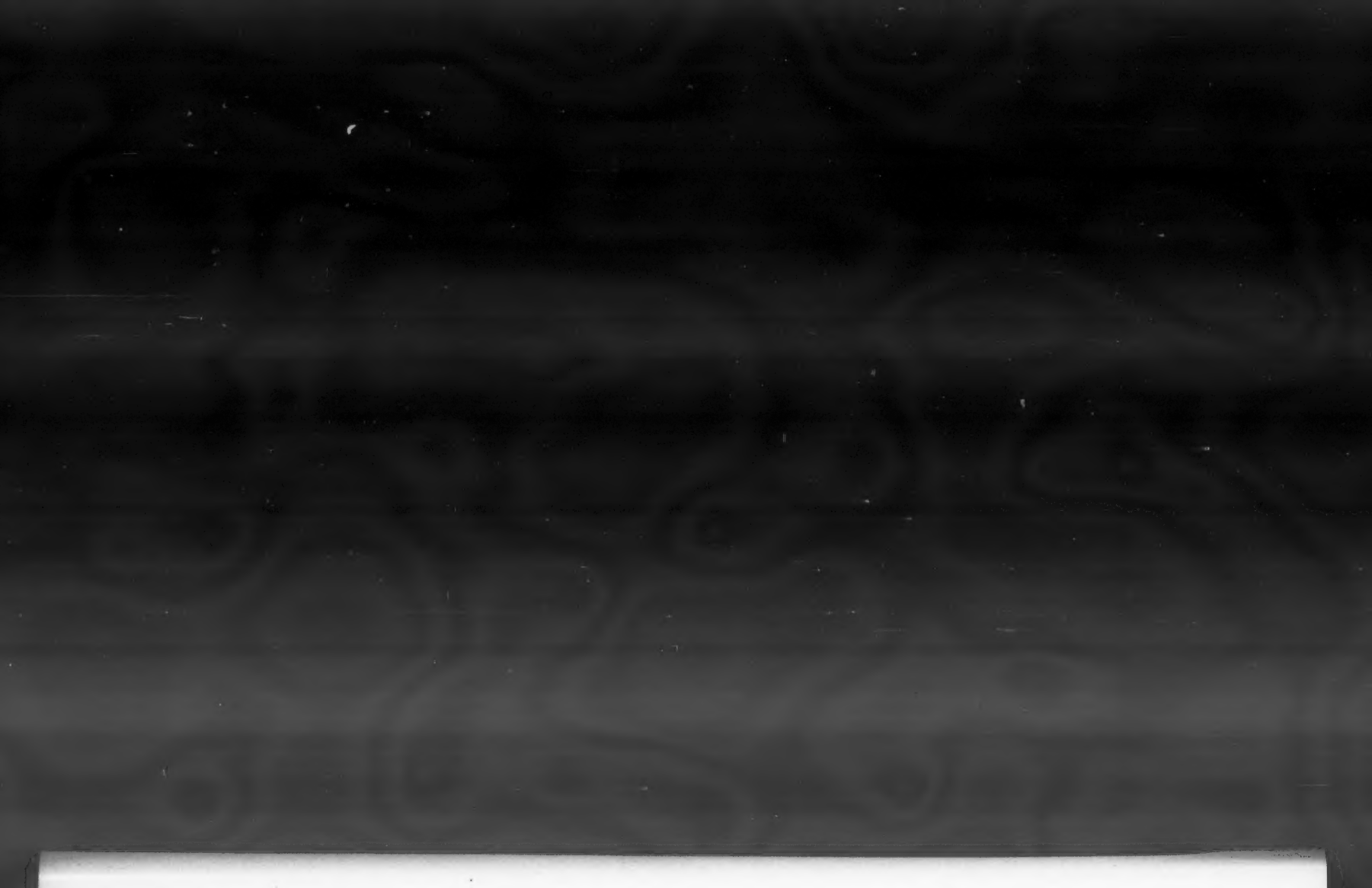
Congdon Benign and Malignant Chordomas

PLATE 125

FIG. 11. Cut surface of tumor removed surgically in case 19. There is encapsulation in some portions of the circumference and none in others.

FIG. 12. Low-power view of the section from which Figures 9, 10, and 13 were taken. Of note are the alveolar growth pattern of the tumor and lack of encapsulation. Hematoxylin and eosin stain. × 10.

FIG. 13. A third area from the same section as Figures 9 and 10 showing a fibrillar portion of the neoplasm. Hematoxylin and eosin stain. × 170.



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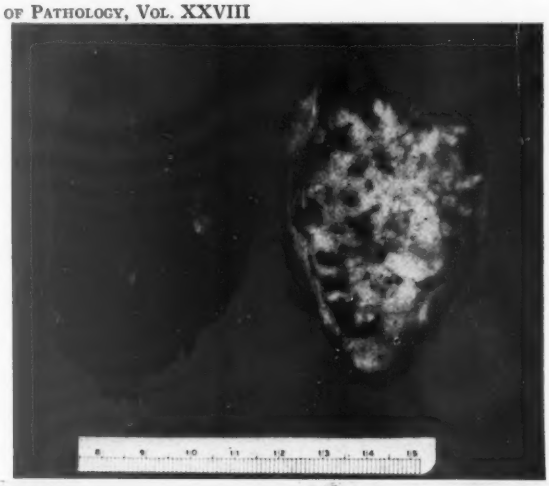

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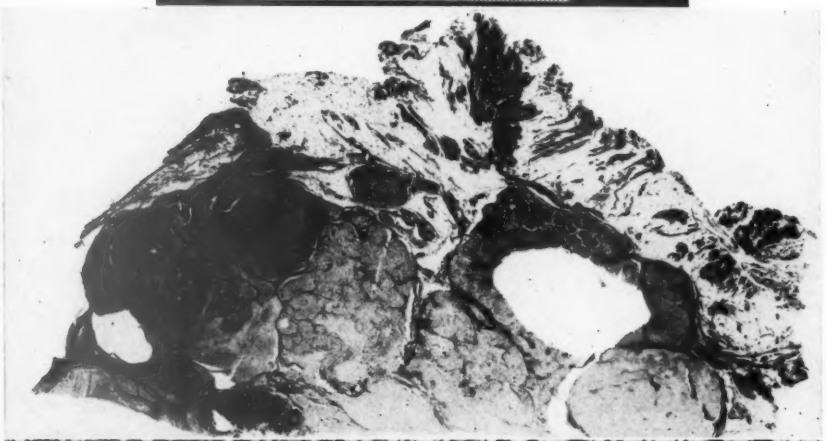

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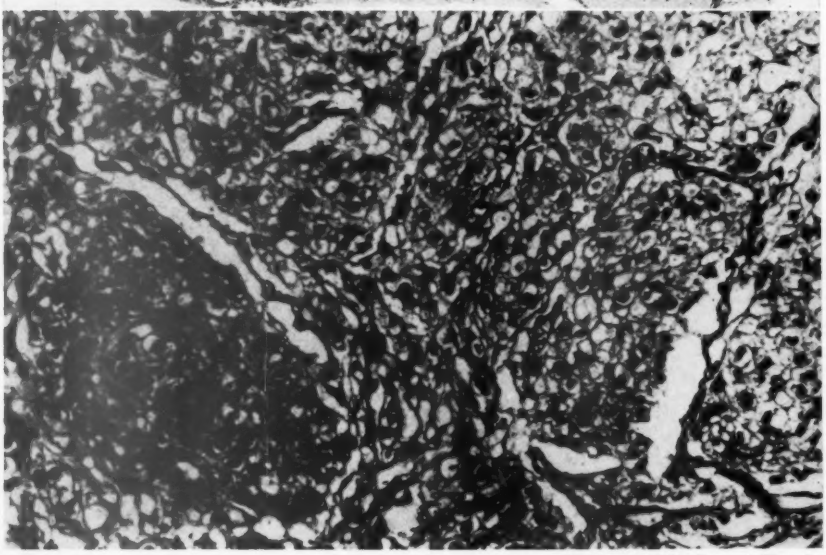

ANITSCHKOW CELL SARCOMA OF THE HEART*

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It is the purpose of this paper to report a primary neoplasm of the heart in which there were areas of Anitschkow cells. This case presents several interesting features in that it is the first reported neoplasm to contain Anitschkow cells and that from it information is gained as to the nature and origin of this disputed cell. Evidence is presented that the Anitschkow cell is not restricted to the heart.

REPORT OF CASE

A 30-year-old white male was admitted to the U.S. Naval Hospital, Camp Joseph H. Pendleton, Oceanside, California, complaining of shortness of breath on exertion and a sensation of fullness and distress in the right upper abdomen and epigastrium. The duration of symptoms was 2 weeks. He was well developed and well nourished and appeared to be acutely and seriously ill. The temperature was 98.8° F.; the pulse rate, 90 per min.; the respiratory rate, 19 per min.; and the blood pressure 110/78 mm. of Hg. On percussion, the heart was slightly enlarged. A harsh systolic murmur and thrill were present over the entire precordium. Distention and enlargement of the neck veins persisted in the upright position. The liver was tender, enlarged, and palpable 6 cm. below the right costal margin. The venous pressure was 190 mm. of water, at rest. Laboratory studies revealed a total white blood cell count of 12,000 per cmm., and a differential count of 5 staff cells, 74 neutrophilic polymorphonuclear leukocytes, and 21 lymphocytes per 100 white cells. The sedimentation rate (Cutler) was 8 mm. in 1 hour. The total red blood cell count, hemoglobin, and results of urinalysis were normal. He developed a leukocytosis of 30,000 per cmm. with a shift to the left, and the sedimentation rate increased to 18 mm. in 1 hour during the course of his illness.

Electrocardiographic studies showed a right bundle branch block and right axis deviation. The initial roentgenogram of the chest was normal. Active rheumatic heart disease was considered the best diagnosis. Dissecting aneurysm of aorta, ruptured infarct of the interventricular septum, and cardiac neoplasm were considered also. The clinical course was one of rapidly progressive right-sided congestive cardiac insufficiency manifested by dyspnea, orthopnea, attacks of cyanosis, pulsating enlargement of veins, left-sided hydrothorax, enlarged tender liver, ascites, and edema of the ankles. He ran a low-grade fever. Roentgenograms of the lung fields remained normal.

A therapeutic test with digitalis aggravated his symptoms. He was given intravenous ACTH (acthar, Armour) by continuous intravenous drip with equivocal improvement. Dyspnea became severe and continuous oxygen administration was necessary.

Two months after the onset of symptoms he suddenly became extremely dyspneic, cyanotic, lapsed into coma, and died in about 12 minutes. The clinical impression was that he had died of massive pulmonary embolism.

* The opinions and views set forth are those of the authors and are not to be considered as reflecting the policies of the Navy Department.

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Necropsy Findings

The necropsy (A-72-51) was performed 14 hours after death. The body measured 73 inches in length and weighed approximately 180 lbs. The face, neck, and upper portion of the thorax were dusky purple.

The *heart*, weighing 450 gm., showed distention of the right auricle and ventricle. The dilated pulmonary artery was completely occluded by a firm, grayish white, nodular mass which projected 3 cm. into the left branch of the pulmonary artery. Attempts to remove this mass were unsuccessful, as it was attached firmly deep in the heart; it was not adherent to the pulmonary artery. On opening the heart by transverse sections through the ventricles, a large, grayish white, nodular, firm, smooth-surfaced, lobulated tumor was found, which distended and filled nearly completely the upper one-half of the right ventricle, and projected 3 cm. through the tricuspid valve into the right auricle. The nodules varied from 1 to 3 cm. in diameter and presented a smooth external surface. A few polypoid cystic structures projected from the surface of the tumor. The cut surface was mainly firm, homogeneous, and yellow white, with a few small hemorrhagic areas. The tumor was covered in some areas by laminated blood clot.

The tricuspid orifice was dilated by the tumor to 5 cm. in diameter. The site of origin of the neoplasm was the upper 4 cm. of the interventricular septum. There was slight invasion of the muscular interventricular septum, and of the lower portion of the anterior and medial wall of the right auricle which resulted in neoplastic tissue lying adjacent to the right side of the root of the aorta. The neoplasm extended along the medial 3 cm. of the right atrioventricular groove, and partially enclosed, displaced anteriorly, but did not enter the right coronary artery (Figs. 1 and 2). There was no invasion of the left side of the heart. The heart showed no other abnormalities.

The *left lung* weighed 700 gm. and the *right lung* 400 gm. There was moderate pulmonary edema and atelectasis of both lower lobes, but no gross evidence of metastatic lesions.

The *liver* weighed 2,150 gm., and showed the changes of severe passive congestion. There was ascites of 500 cc. and bilateral hydrothorax of 400 cc.

Microscopic Findings

Heart. Sections of the heart stained with hematoxylin and eosin revealed a neoplasm composed of closely packed spindle cells arranged in sheets. In some areas columns of cells interlaced to give a "herring bone" pattern (Fig. 5). The majority of the cells contained uniform

oval nuclei with fine chromatin particles and indistinct nucleoli. The cytoplasm was indistinct. The most striking microscopic feature was the presence of numerous foci of typical Anitschkow "myocytes." The nuclei of these cells contained a prominent, basophilic, longitudinal, serrated chromatin bar from which radiated fibrils of chromatin. The majority of these fibrils extended to the inner surface of a distinct nuclear membrane. The remainder of the nucleus about the chromatin bar was clear (Figs. 3 and 4). The nuclei of these cells when cut in cross section showed a circular mass of chromatin from which chromatin fibrils extended through a clear area to reach the inner surface of the nuclear membrane. These cells had an "owl's eye" appearance. The stroma consisted of fine, wavy, eosinophilic collagenous fibrils, which wrapped around the cells. These fibrils occasionally were condensed to form wide bands of dense collagenous tissue in which individual fibrils could still be distinguished. The neoplasm contained numerous capillaries which were dilated near the external surface of the neoplasm and around areas of necrosis. Mitotic figures were less frequent in the foci of Anitschkow cells than in other portions of the neoplasm. In some areas neoplastic growth was more active as evidenced by numerous mitotic figures; such areas compressed adjacent regions of less actively growing neoplasm. Hemorrhagic foci were present, often associated with hemosiderin-filled macrophages. There were large eosinophilic areas of necrosis, without inflammatory reaction, in which only the vague outlines of neoplastic cells could be recognized. The external surface of the tumor was covered by laminated blood clot, a thin layer of fibrin, or a zone of condensed neoplastic cells. Myocardial fibers showed degenerative changes where the neoplastic tissue invaded the interventricular septum, and where it enclosed papillary muscles and trabeculae (Fig. 6). These degenerated muscle fibers showed loss of myohemoglobin and contractile elements, vacuolization of the cytoplasm and karyolysis; the interstitial fibers were continuous with the collagenous structure of the neoplasm. The degenerated muscle cells resembled somewhat the "spider cells" seen in congenital rhabdomyoma. In some areas there was complete loss of myocardial fibers with replacement by fibrous tissue. In these fibrous areas there were clumps of lipochrome pigment, evidence of previously existing myocardial fibers. There were a few scattered cells of unknown nature that had abundant cytoplasm, which stained red with hematoxylin and eosin and with Giemsa's stain, and orange with Mallory's phosphotungstic acid stain.

The cystic structures observed grossly to be projecting from the sur-

face of the neoplasm showed microscopically an external layer of neoplastic cells, with abundant formation of collagen, a middle layer of necrotic tumor cells, and an inner layer of fibrin. In some areas it appeared that fibroblasts derived from the neoplasm had grown along fibrin threads in an attempt to organize the blood clot.

Wilder's reticulum stain revealed abundant fine, wavy, reticular collagenous fibers in parallel arrangement. These fibers stained orange with Mallory's phosphotungstic acid stain, blue with Masson's trichrome stain, and red with van Gieson's stain. The reticular fibers of the neoplasm had the same appearance as those of normal myocardium, with which they were continuous where the neoplasm invaded the myocardium. The chromatin bar of the Anitschkow cell was particularly well stained by Giemsa's stain. Giemsa's stain revealed one to five small spherical nucleoli in the predominant neoplastic cells, and none in the Anitschkow cells.

Sections of *lung* revealed several small foci of neoplastic cells similar to those of the neoplasm in the heart. These cells were present in the interstitial tissue of the lung and had apparently lodged in septal capillaries, widened the septa, but had not invaded the alveoli. No Anitschkow cells were present in these metastatic lesions.

Sections of *liver* and *spleen* showed the pathologic changes of severe passive congestion.

Pathologic Diagnoses. Primary Anitschkow cell sarcoma of heart with massive obstruction of pulmonary artery by tumor. Metastases to lung. Bilateral hydrothorax. Ascites. Pulmonary edema. Passive congestion of viscera.

Discussion

This case represents the first reported neoplasm of the heart, or of any tissue, to contain Anitschkow cells. Mahaim[1] in his extensive study of tumors of the heart, Yater[2] who reviewed all primary neoplasms of the heart up to 1931, and, more recently, Prichard,[3] do not mention tumors of the heart composed of Anitschkow cells. That these Anitschkow cells are neoplastic cells there can be little doubt, as they were found in numerous large foci within the neoplasm, the nuclei had the same spindle shape, and the collagenous stroma was the same as the more common neoplastic tissue. The neoplasm was malignant as evidenced by the metastatic lesions in the lungs, numerous mitotic figures, invasion of the interventricular septum, and the rapid growth of the neoplasm manifested by the extremely short duration of 2 months from the onset of symptoms to death.

There has been considerable variance of opinion as to the origin of

the Anitschkow "myocyte," a brief discussion of which will be given later. The microscopic findings in this case indicate that the Anitschkow cells of this neoplasm originated from the interstitial collagenous connective tissue of the heart. Evidence for this view is that the staining reactions and appearance of the stroma of the neoplasm were those of collagenous tissue, and similar to the collagenous tissue in the myocardium adjacent to the neoplasm. The neoplastic reticular fibers and the interstitial tissue of the heart stained red with van Gieson's stain, blue with Masson's stain, and yellow-orange with Mallory's phosphotungstic acid stain, whereas the myocardial fibers stained respectively yellow, red, and purple with these stains. Reticulum stains revealed the reticular fibers of the neoplasm to be fine, wavy, and similar to the reticular fibers of the heart, with which they were continuous. Other evidence for the origin of this neoplasm from fibrous connective tissue was the pattern, which was one of interlacing columns of spindle cells to give a "herring bone" effect; the uniform spindle-shaped nuclei, without formation of giant cells or the formation of bizarre tumor cells are more characteristic of fibrosarcoma, than of rhabdomyosarcoma or leiomyosarcoma. None of the neoplastic cells in this case contained myohemoglobin or exhibited myofibrils. Anitschkow emphasized that the "myocyte" was incapable of forming myohemoglobin. The origin of this neoplasm from myocardial interstitial tissue is not incompatible with Anitschkow's original view on the origin of the "myocyte." Anitschkow stated that the "myocyte" had two origins, one from cells in the interstitial tissue of the heart, and the other from degenerating myocardial fibers. Anitschkow believed, however, without any definite proof, that the interstitial "myocyte" was also of myogenous origin. He also stated that, in one stage of the reaction to injury of the heart, the "myocytes" changed into cells indistinguishable from fibroblasts. According to Wenezianowa-Grusdkowa,[4] the Anitschkow "myocyte" has phagocytic activities, but the cells in this case did not show phagocytosis, even in areas in which there were free hemosiderin granules. One must conclude, at least for this case, that the Anitschkow cells were derived from fibrous tissue, and that the neoplasm represents an unusual variety of fibrosarcoma.

There have been many theories and experimental studies on the origin of the Anitschkow "myocyte." It has been believed to originate from cardiac muscle, cardiac fibrous tissue, smooth muscle of blood vessels, and cardiac reticulo-endothelial elements. As a result of these beliefs the cell has been variously named, "myoblast" (von Oppel[5]), "cell of myogenous origin"; "myocyte" (Anitschkow[7]); "cardiac histio-

cyte" (Clawson[14]); and "cardiac reticulocyte" (Ehrlich and Lapan[6]). The first work on the Anitschkow "myocyte" was done by von Oppel[5] who described the origin of this cell as follows: After injury of the myocardium by a needle the myocardial fibers lost their cross striations and the cytoplasm became granular; concurrently the nuclei enlarged and assumed an oval shape. The contractile elements gradually disappeared and the nucleus was left free, surrounded by a layer of sarcoplasm. In some of these nuclei there was a peculiar change in that the chromatin became arranged in a condensed longitudinal bar, or a crescent, or in two clumps. Division of these nuclei was noted, possibly by amitosis, since no mitotic figures were described. Later, these cells of myogenous origin merged with and could not be distinguished from fibrocytes.

Anitschkow[7] extended and confirmed the work of von Oppel,[5] and Saltykow.[8] He found myocytes normally in the interstitium of the heart, and believed that these interstitial cells were of myogenous origin. He noted that there was complete degeneration of myocardial fibers immediately adjacent to foreign bodies composed of threads impregnated with celloidin whereas those myocardial cells further removed from the foreign body showed loss of myohemoglobin, retention of the sarcolemma, and condensation of the chromatin of the nucleus to form the characteristic chromatin bar. He also noted that in an intermediate stage of the reaction to the foreign body, these "myocytes" were indistinguishable from fibrocytes. He was undecided as to whether there was an actual transition of myocytes to fibroblasts, or whether the fibroblastic appearance was transient.

Jacki[9] studied a case of concurrent rheumatic myocarditis and rheumatic nodules in the galea aponeurotica. She stated that the Anitschkow "myocyte" was derived from cardiac fibers. The basis for this belief was that the histologic appearance in the myocardial and galeal lesions was similar except for the presence of Anitschkow myocytes in the former and their absence in the latter. Karsner and Dwyer[10] found Anitschkow "myocytes" in experimentally produced infarcts of the heart after 24 hours. They stated that similar peculiar nuclear changes occur in cardiac muscle, macrophages, and connective tissue. Wenezianowa-Grusdkowa,[4] on the basis of intravital staining of the heart following injury, concluded that the Anitschkow "myocytes" were derived from macrophages (histiocytes), in a manner similar to the derivation of myophages in the degeneration of skeletal muscle as shown by Taratynow.[11] Semsroth and Pool,[12] studying a cardiac

wound in a 10-year old girl, were of the opinion that the myocytes were derived either from blood vessel endothelium or from fibroblasts.

Hesse and Hesse,[13] from a study of human hearts after trauma, concluded that the Anitschkow "myocytes" probably were derived from degenerated muscle cells. They emphasized that the Anitschkow cells are most frequently found in areas of degenerating muscle and in areas where there is a merging of fibrous tissue and cardiac muscle. In our case, although Anitschkow cells were found in the neoplasm adjacent to cardiac muscle, they were found also in foci far removed from cardiac muscle. Clawson[14] stated that the Anitschkow "myocyte" should be considered a cardiac histiocyte, since the cell appears to be derived from cardiac interstitial tissues. However, Clawson made no distinction between the non-phagocytic collagenous reticulum composed of fibrocytes of the heart and the phagocytic reticulo-endothelial system. Ehrlich and Lapan[6] pointed out that the Anitschkow "myocyte" is a normal constituent of the human and vertebrate heart during the embryonal and post-embryonal stages of development, is a part of the supporting tissue of the heart, and belongs to the fixed elements of the reticulo-endothelial system. They showed that the Anitschkow "myocyte" is normally found in the interfascicular planes, in the fibrous core of the cardiac valves, and within the muscle fasciculi between the individual cardiac muscle fibers.

Against the theory that the Anitschkow "myocyte" is derived exclusively from cardiac muscle fibers is the work of Wätjen,[15] who found Anitschkow "myocytes" in the epicardium in a case of rheumatic heart disease, and Semsroth and Pool,[12] who found Anitschkow cells at the base of vegetations on the mitral valves. In both of these locations there is no cardiac muscle tissue present. Similarly, in our case all evidence points toward origin of the Anitschkow cells from fibrous tissue. Certainly, this neoplasm did not have the appearance of one derived from the reticulo-endothelial system, or from smooth muscle, or from striated muscle. It is possible that this peculiar nuclear formation is not characteristic of any one cell, but that it represents a degenerative change of cells of many types within the heart, and of tissues in other parts of the body.

As to the formation of the Anitschkow cell, one may speculate that the changes are a result of hydropic degeneration in a cell the chromatin of which is fixed at the extremities of the nucleus. Such a nuclear formation could be produced by imbibition of fluid into the cytoplasm, and then through the nuclear membrane. Evidence for this speculation

is the clear cytoplasm of the Anitschkow "myocyte" and the clear areas on either side of the chromatin bar. The chromatin may at one time have been adjacent to the nuclear membrane and as the chromatin condensed into the central longitudinal bar radiating fibrils were formed. The Anitschkow "myocytes" in this neoplasm were particularly prominent in areas where the cells were sparse, and in which there was edema of the stroma. However, in other areas without edematous stroma, foci of Anitschkow cells were present. They were not more numerous around areas of necrotic neoplasm. Anitschkow was of the opinion that the nuclear changes in the "myocyte" were an unusual type of pyknosis, and that the cells showing the chromatin bar were found in myocardial fibers undergoing degenerative changes manifested by loss of myohemoglobin about foreign bodies in the heart.

The Anitschkow "myocyte," although often found in the Aschoff body and myocardium in rheumatic fever, is certainly not specific for rheumatic fever. Clawson[14] found Anitschkow myocytes in Aschoff nodules in all of 36 cases of rheumatic fever. Ehrlich and Lapan[6] found Anitschkow myocytes to be a normal constituent of the heart, and present also in hearts from cases of sepsis, meningococcic bacteremia, scarlet fever, periarteritis nodosa, and subacute bacterial endocarditis. There are many reports of Anitschkow myocytes about experimentally introduced foreign bodies in the heart. Lenke and Loewe[16] found Anitschkow myocytes in spontaneous pancarditis in mice.

We have recently been able to obtain a section of pleura showing extracardiac Anitschkow cells through the courtesy of Dr. Lalla Iverson[17] and the Armed Forces Institute of Pathology. This case (AFIP Accession no. 489353), as demonstrated to us by Dr. Iverson, showed unequivocal Anitschkow cells with the typical chromatin bar, in the mesothelial cells of the visceral pleura. This finding is at variance with that of Clawson[14] who stated that the Anitschkow "myocyte" was specific for the heart.

Prichard[3] collected 113 cases of primary sarcoma of the heart in the world literature and gave the following data: The age distribution ranges from 3 days to 79 years. The sex distribution is approximately equal. The weight of the heart is higher in cases of sarcoma than of myxoma. Over one-half of the sarcomas arise in the right side of the heart. Most of the tumors have been infiltrative or sessile but 20 per cent have been polypoid. Distant metastases have occurred in over 30 per cent of cases. Histologically, most of the neoplasms have been

composed of "spindle" cells, and the diagnoses have included fibrosarcoma, fibromyxosarcoma, myxosarcoma, and leiomyosarcoma. Next in frequency were "round cell" sarcomas designated either by that term or as lymphosarcoma, reticulum cell sarcoma, or stem cell lymphoma. Rhabdomyosarcoma and angiosarcoma have been described. Our case conforms to the most common type, and is distinguished only by the presence of the Anitschkow "myocytes."

The clinicopathologic correlation is rather easily explained in retrospect. The enlargement of the heart was due to the expansive growth of the neoplasm. The dilated right auricle, dyspnea, orthopnea, and enlargement of the liver were due to passive congestion, the result of an obstructive tumor mass in the region of the tricuspid valve. Right bundle branch block was the result of invasion of neoplasm into the interventricular septum. An indication for the diagnosis of primary neoplasm of the heart, and against the diagnosis of rheumatic heart disease was the aggravation of cardiac symptoms after the use of digitalis. Yater[2] placed considerable emphasis on this feature in the clinical diagnosis of primary neoplasms of the heart. Also, the initial normal sedimentation rate, lack of anemia, slight fever, rapid course, clear lung fields, and failure to respond to ACTH were against the diagnosis of rheumatic heart disease, and in favor of a diagnosis of primary neoplasm of the heart.

Summary

The first case of Anitschkow cell sarcoma of the heart is reported.

Evidence is offered that the Anitschkow cells in this neoplasm are derived from the collagenous connective tissue of the heart, and therefore that this neoplasm represents a unique type of fibrosarcoma.

It is suggested that the Anitschkow type nucleus is not specific for any one cell, but represents a type of nuclear degeneration, which may be found in cells derived from several types of tissue.

The Anitschkow cell is not restricted to the heart, since mesothelial cells of the visceral pleura may have a similar appearance.

We wish to thank D. K. Miller, HMl, USN, for the photographs.

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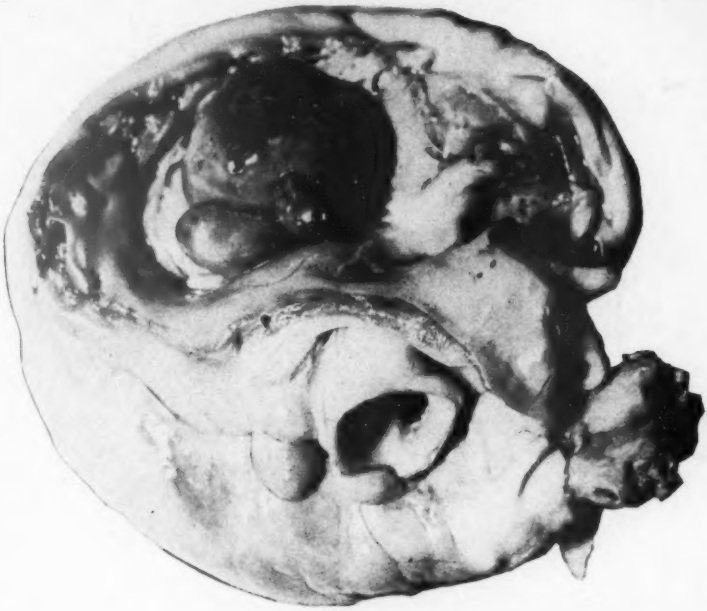
DESCRIPTION OF PLATES

Plate 126

Fig. 1. Superior view of the heart. The right auricle has been removed to reveal the tumor projecting through the tricuspid valve. Of note also is the tumor projecting from the severed pulmonary artery.

Fig. 2. The under surface of the specimen shown in Figure 1. The neoplasm originates from the interventricular septum and nearly completely fills the right ventricle.

1



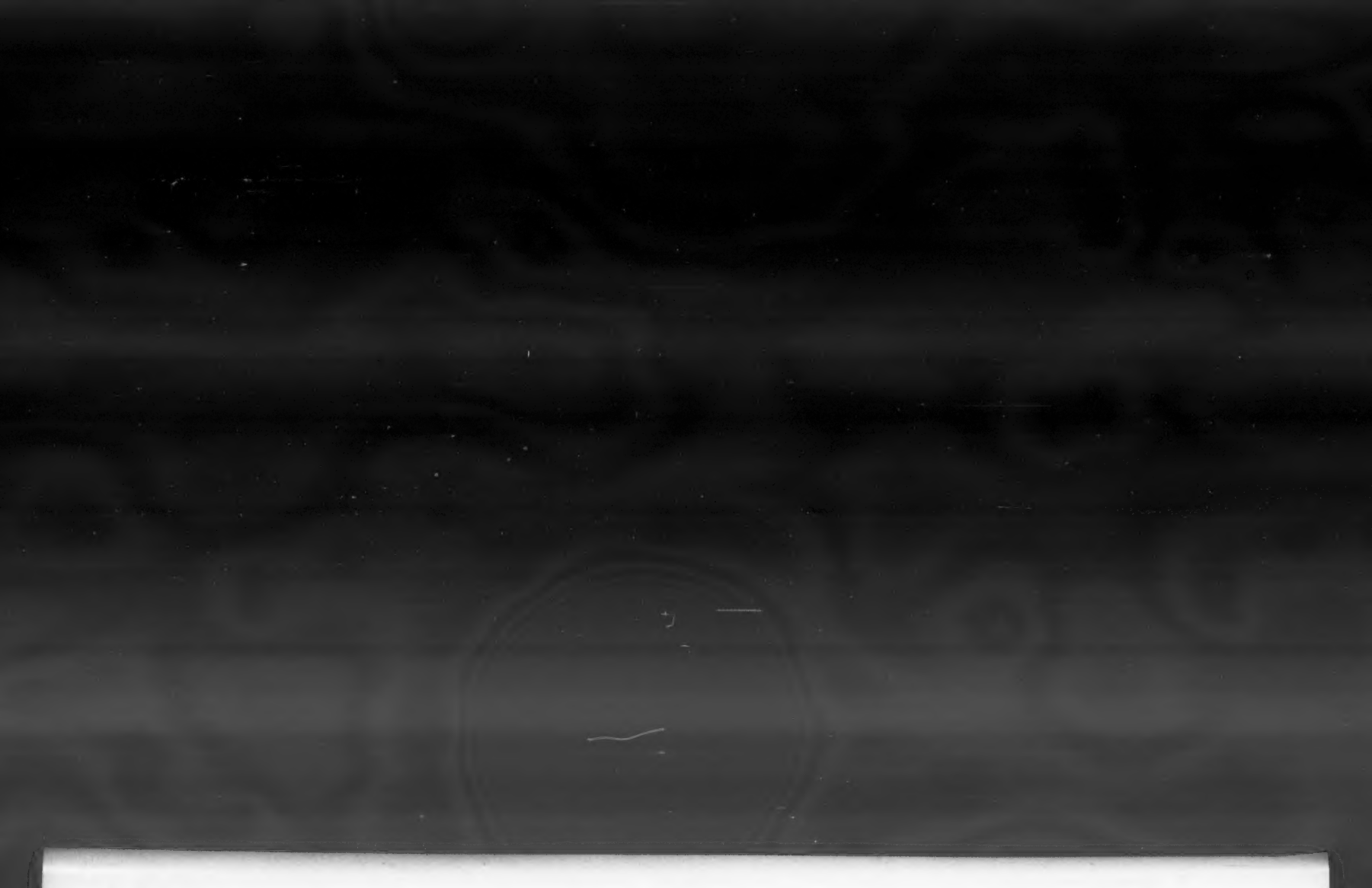
2

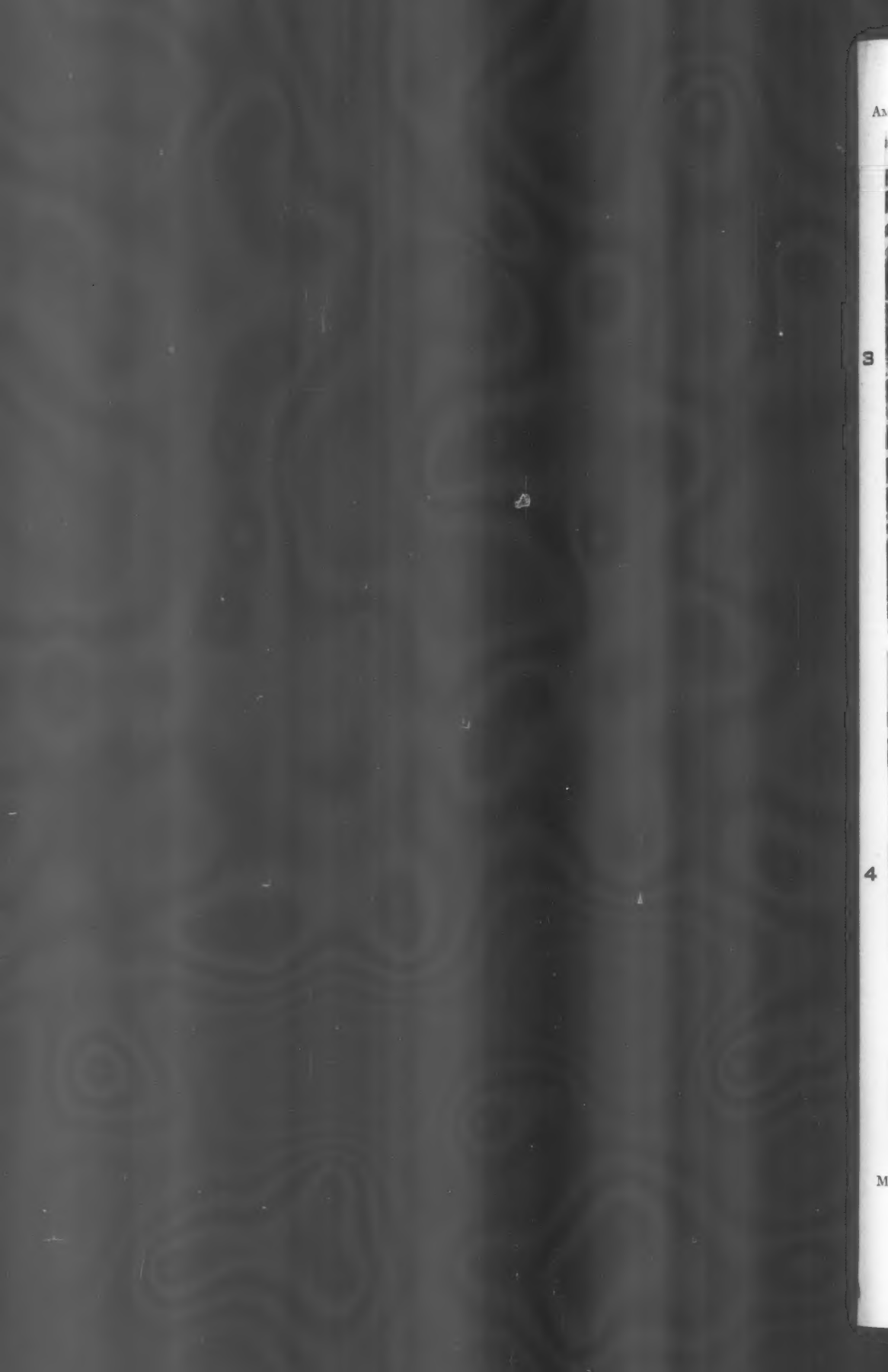
Mainwaring and Ayres Anitschkow Cell Sarcoma of Heart

PLATE 127

FIG. 3. Neoplastic Anitschkow cells. Of note is the prominent longitudinal chromatin bar. × 500.

FIG. 4. Detail of Anitschkow cells. × 1200.





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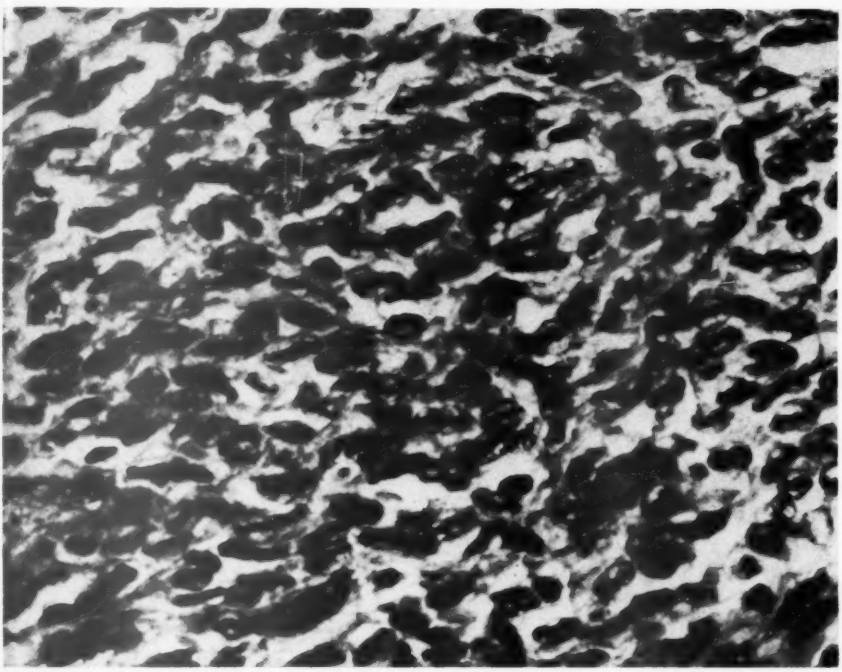

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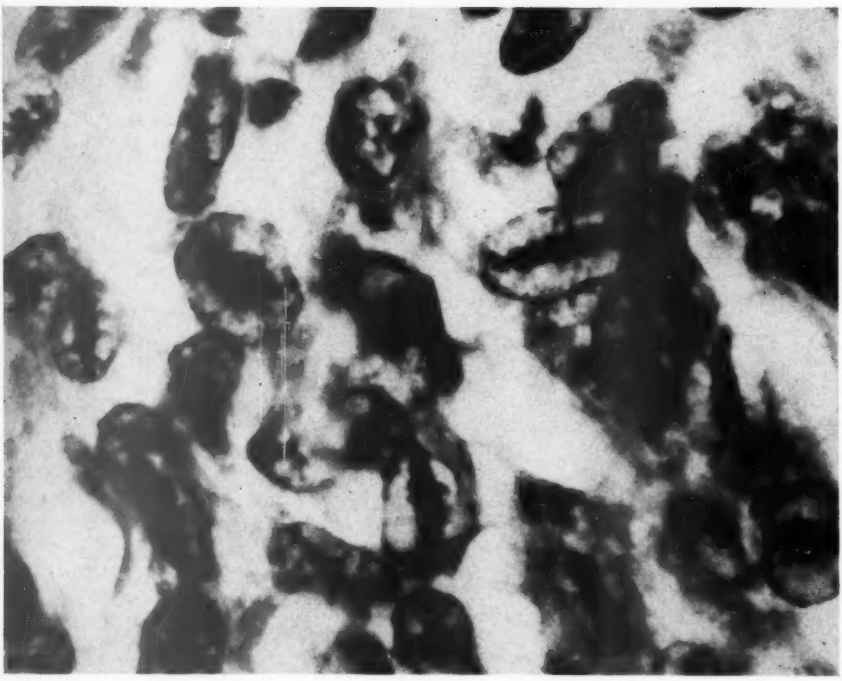
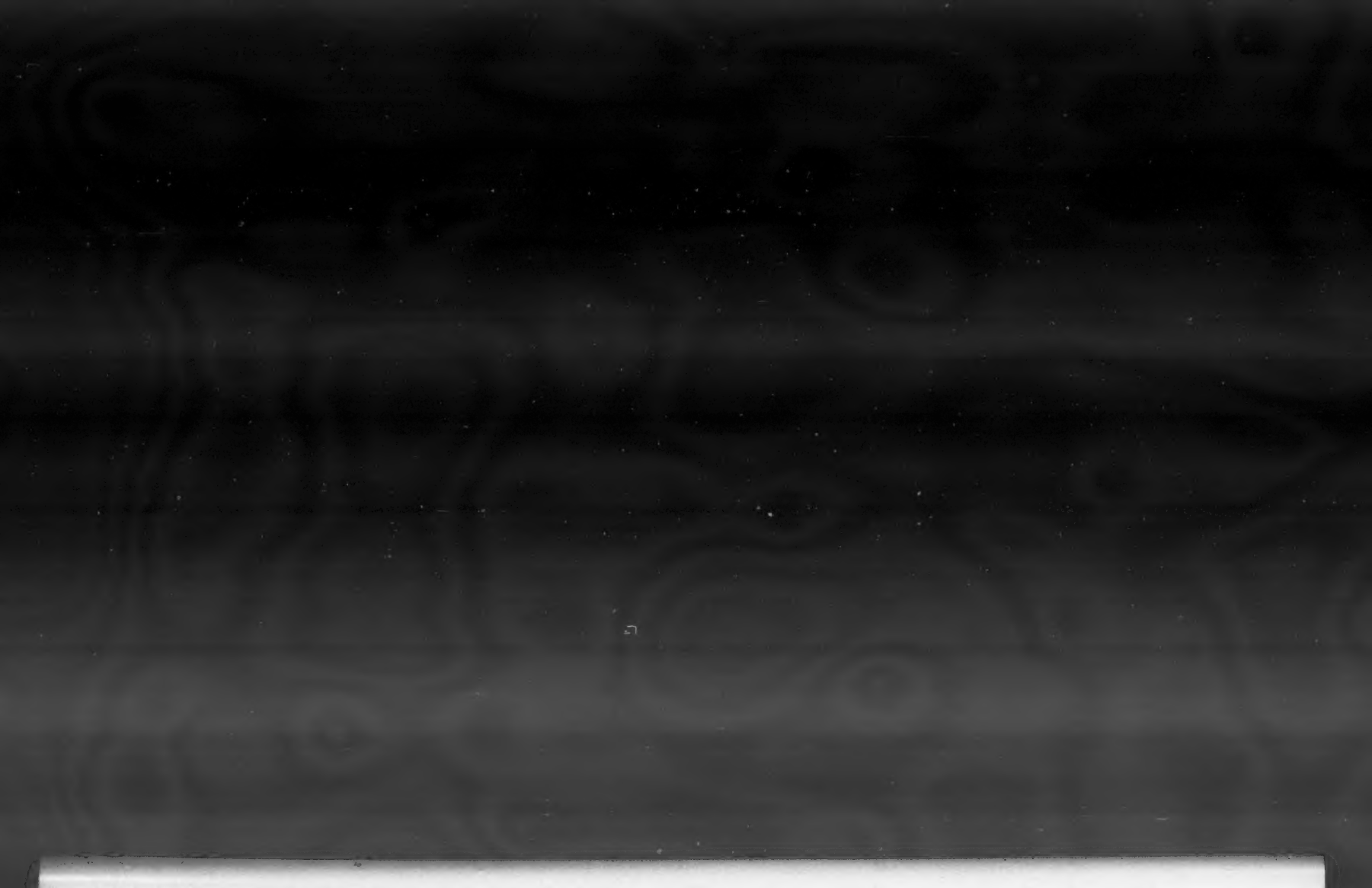


Mainwaring and Ayres Anitschkow Cell Sarcoma of Heart

PLATE 128

FIG. 5. Area of neoplasm in which there are no Anitschkow cells. The uniform oval nuclei and pattern of interlacing cells favor a diagnosis of fibrosarcoma.

FIG. 6. Gradual merging of the neoplasm with the myocardium. There are degenerative changes in some of the cardiac fibers.



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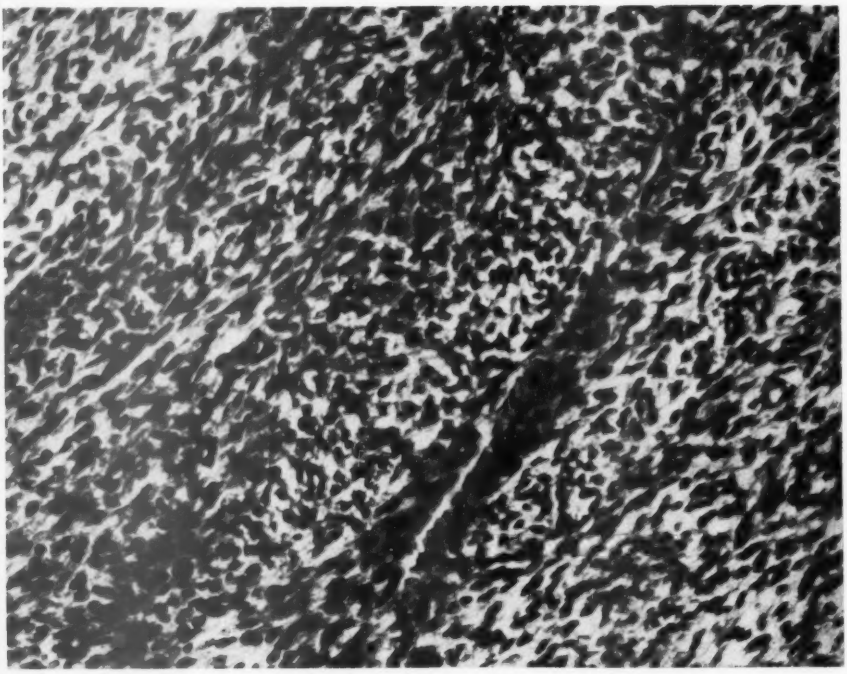

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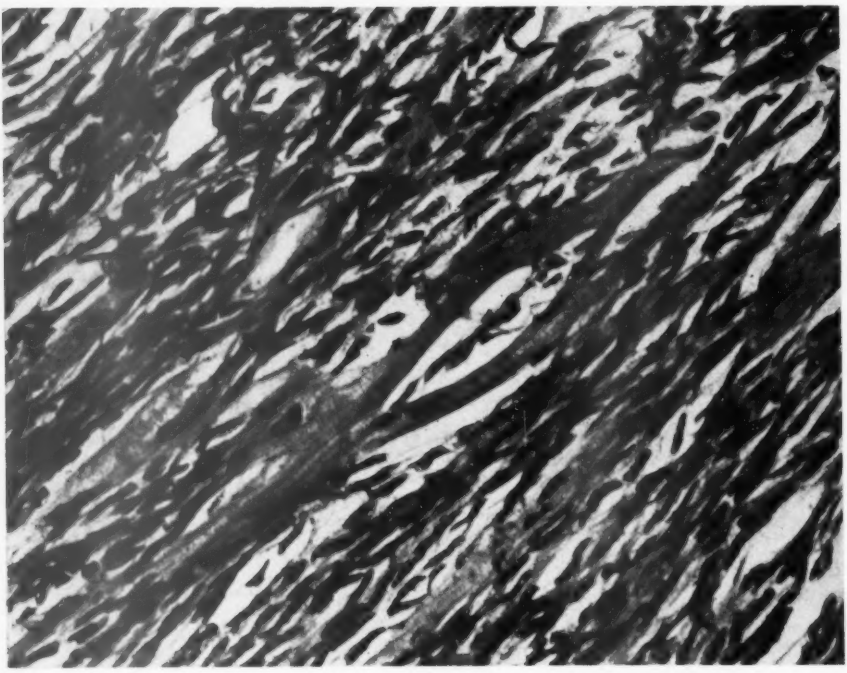

Mainwaring and Ayres Anitschkow Cell Sarcoma of Heart

FURTHER PILOT ECHOGRAPHIC STUDIES ON THE HISTOLOGIC STRUCTURE OF TUMORS OF THE LIVING INTACT HUMAN BREAST*

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The object of this study was to examine further the effect of living intact tumor tissue of the human breast on a pulsed electrosonic beam directed into tumors from the overlying skin.[1] More specifically, this investigation was planned to determine the preoperative diagnostic possibilities of the method on the basis of the histologic structure of palpable lesions, with a view to future applications to other sites. The investigation was not planned to detect tumors and was not necessarily intended to replace existing methods of diagnosis of breast lesions.

HISTORY OF THE METHOD

The principle of creating bursts of sound energy and studying the echoes returning has been used for years in the detection of flaws in metals. The highest frequency used commercially is 5 megacycles. Ludwig and Struthers[2] reported the application of the commercial machine to the biologic field. They demonstrated that gallstones and foreign bodies buried in the muscles of dogs could be detected at a frequency of 2½ megacycles.

However, theoretically, the approach to the examination of tissues in terms of cellular composition required a considerably higher frequency, greatly increasing the technical difficulties. A machine specifically for the simulation of "radar" on a small scale was developed by the U.S. Navy during the last world conflict. This complex ultrasonic training machine operated at a frequency of 15 megacycles. Thus the opportunity arose to carry out pilot studies on the measurements and echo-producing properties of biologic tissues, including a stomach containing a carcinomatous ulcer freshly removed at operation.[3]

Encouraged by striking differences observed in echo patterns of the carcinomatous ulcer, the infiltrated stomach wall, and the normal stomach wall used as a control, pilot work was carried out on fresh malignant cerebral tissue.[4,5] It was found possible to detect malignant tissue in the brain substance through the dura mater post mortem.

Experiments were carried out on the brains of living animals,[6] and

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on the living intact human arm[1] to determine possible effects. No harmful effects from the method have been observed to date.

A limited clinical trial was attempted.[1] The histologic structure of 2 nodular lesions of the human breast was correctly forecast before biopsy in terms of malignancy and benignancy without apparent harm to the patients. Results of further pilot work carried out on the human breast, using a machine specifically designed for biologic application, are recorded in this report. This investigation is not concerned with detecting unsuspected lesions but with the histologic differentiation of living intact tumors.

Principle

Sound energy can be produced from electrical energy by means of the piezo-electric phenomenon. Piezo-electric substances can be mechanically deformed by application of electric charges. Conversely, when piezo-electric substances are mechanically deformed, electric charges are produced. Sound waves can be produced by mechanical motion so that a piezo-electric substance can convert sound energy into electrical energy or, conversely, can convert electrical energy into sound energy. When a piezo-electric substance is arranged for the production or reception of sound in electrosonic terms, the name electro-acoustic transducer is applied to the instrument. By suitable design, a narrow beam of sound energy can be produced from such a transducer. This sound beam can be directed into a system under examination. Two technics can be applied. In the first, termed a transmission technic, the sound energy from the transmitting crystal can be driven through the system under examination and "collected" by a receiving crystal placed at the point of exit of the sound beam from the system. From this arrangement the amount of sound energy absorbed by the system between the two transducers can be observed. This type of observation is termed a measurement of attenuation of the sound beam. The value of such a system will depend upon the amount of information required. If the sound beam is moved through the tissues, a record of intensity variation analogous to an x-ray can be obtained. The transmission technic has been attempted in order to outline the ventricles of the brain in the living human subject.[7-9]

The second technic is termed reflection, and is the type believed more useful where more information is desired, as in the present study. In this method, sound energy is driven into the tissues, and the echoes returning to the transmitting transducer from the interfaces between the various elements in the path of the sound beam are studied. It is obligatory with this technic to pulse the sound energy so that a time

interval is available for the detection of the returning echoes just as in the case of shouting at a mountain face where a pause is necessary in order to hear the echoes. Thus, the time of exposure of the tissues to the sound beam is short. With this arrangement, at a suitable frequency, distances from the surface of the interfaces, in addition to more detailed information about attenuation of the sound beam by the various tissue elements, can be obtained.

Discussion of Possible Harmful Effects

A review of the extensive literature, going as far back as 1928, on the damaging effects of ultrasonic energy is beyond the scope of this communication. Much of the work on damaging effects is in our opinion not directly applicable to our investigation, since the operation of our machine is without precedent in the biologic field. Results of workers specifically interested in damaging effects on tissues are extremely difficult to apply because of the great differences existing in the conditions of experimentation. The result of the intensive work on damage has tended to implant the impression that ultrasonic energy must be handled with caution. When this impression is coupled with the all too recent memory of the terrible sequelae of x-radiation unsuspected by pioneer workers, it is not surprising that a very cautious attitude toward the diagnostic possibilities of ultrasound should be manifest.

The suffering of the early workers with x-rays was not in vain, since it has been possible to control x-radiation to an apparently "safe" level for therapeutic and diagnostic procedures, though even today a casual observer of the skin of some patients after deep x-ray therapy would conclude that the skin had been "damaged permanently." It is therefore necessary to consider carefully what is meant by the words "harmful" and "damage." Such factors as time scale, completeness of recovery, restoration of function, and the object in mind in risking the damage, must be taken into account.

No late sequelae comparable to those seen after x-radiation have yet been demonstrated with ultrasonic energy. Theoretically, there is no reason to expect such sequelae since ultrasonic energy is a form of mechanical energy. The pressure wave produced as sound energy causes displacement in the medium and imparts velocity and acceleration to particles composing the medium. The passage of the pressure wave gives rise to internal friction producing heat over the period of application; in addition, dissolved gases may be released from liquid media and tearing apart of the medium may produce cavitation. If the

medium is not homogeneous, as with tissues, local concentration of the effects can occur.

Lynn and Putnam[10] described the histologic effects of high intensity ultrasonic energy at a frequency of 835 kilocycles on the scalps, skulls, and brains of dogs, cats, and monkeys at 10 to 15 minute exposures. The end result was dry gangrene with sequestration of the exposed area.

Because of the unusual operation of our machine at high frequency and of the short, widely spaced pulses, the absence of specific precedent in the literature made extension of other work impossible in the assessment of possible damage. Even had it been possible to extend previous fundamental work, the practical difficulties of measuring sound intensities with our machine would introduce further uncertainty.

The complexity of the problem of damage and the understandable uncertainty of expert opinion forced a direct biologic approach. Accordingly, since no obvious damage was observed in the original pilot experiments in freshly removed tissues, direct application of the echoscope to the exposed brains of animals[6] was carried out. The animals recovered from the anesthetic and maintained unimpaired function. Sacrifice and microscopic examination of the brains at suitable intervals up to several weeks after exposure failed to produce any evidence of damage.

It seemed a reasonable risk to expose the extensor muscles of the left arm of one of us[1] for a 30-minute period. No sensations of heat or pain were experienced. There were no immediate after-effects and no sequelae have appeared to date (20 months later).

It was therefore possible to make a cautious approach to the patient. No complaints of pain were received from any of the patients in this series, either at the time of application or subsequently. No sensations or complaints were admitted upon being questioned. One normal breast exposed for short periods during "tuning-up" experiments is lactating efficiently at the time of writing (8 months after exposure). The living human brain has been exposed through the dura mater during experiments aimed at localization and diagnosis of tumors at operation. No unusual microscopic findings were reported in the removed specimen (glioblastoma multiforme). A scientific evaluation of loss of function was impossible owing to the effects of the operation from which the patient recovered "uneventfully."

Sound Intensity Used in the Experiments

Peak Power. The power actually transmitted while the crystal is vibrating is called the peak power. The maximum figure used in our

experiments, based on calculations assuming a uniform sound beam, is 644 watts per square cm. The value is higher than that reported by most investigators, but the peak intensity is applied for only one-half millionth of a second. We believe that various workers have shown that greater intensities can be used with short exposures than can be used continuously. Fry *et al.*[11] worked on intact frog spinal nerves, and Hueter and co-workers[8] on human periosteal pain thresholds. Unfortunately, their results are not directly applicable to our extremely short exposures.

Average Power. The peak power averaged over a cycle of operation is based on an equivalent energy concept. The average intensity at the surface of our patients was similarly calculated as not more than 1.3 watts per square cm. This figure is below the human periosteal pain threshold found by Hueter and Bolt.[9] We have tried the echoscope on our own tibiae under comparable conditions and have not experienced pain.

It should be noted that our figures are probably high because harmonic voltages across the crystal give the very high peak voltages used in the calculations. Harmonic voltages contribute very little acoustic output.

We think at present that only direct biologic confirmation, such as already described, can give reliable indications of safety. A cautious but positive approach to an area of the patient provided with sensory organs responsive to heat and pain, after all advantage has been taken of the experimental animal, is recommended for testing untried ultrasonic apparatus. In the final test of safety, someone has to be the last link in the chain. We consider our echo-ranging studies as concerned with the effect of tissues on sound rather than the converse.

Terminology

When the sender-receiver unit was designed for clinical work, the name ultrasonoscope[4] was originally used. The words ultrasonography and ultrasonogram were coined in a later publication.[1] It is proposed to simplify the terminology and to refer to the ultrasonoscope as the echoscope, to correspond with the word stethoscope. The electronic machine will be referred to as an echograph and the records of the echographs produced by the machine will be referred to as echograms to correspond with the terminology used in electrocardiography. The entire subject of sound reflection from biologic tissues can be called echography. Recent applications of radar technics[12] make it necessary to introduce further terminology.

Sound energy can be driven into tissues in a narrow beam as de-

scribed, but, also, this narrow beam can be moved through tissues to record continuously the pattern traced out by the returning echoes according to the structure of tissues. Therefore, the echographic structure of tissues can be obtained in one dimension, in a manner analogous to a needle biopsy, or in two dimensions, in one plane. Accordingly, the concepts of uni-dimensional and two-dimensional echography with the corresponding nomenclature can be introduced. Further developments could produce three-dimensional echography.

This communication is concerned mainly with uni-dimensional echography at a frequency of 15 megacycles per second, though some pilot two-dimensional echograms are shown in Figure 8 (case 6) to show how further information can be obtained from biologic tissues.

The Apparatus

The arrangement of the apparatus designed for clinical research is shown in Figure 1. It should be noted that the apparatus was built primarily for general research and can be designed in a more compact form for specific application. The echoscope can be seen clamped to the right hand side of the table top. To the left is the cathode-ray oscilloscope with the camera in position for recording.

The echoscope (ultrasonoscope) has been described elsewhere[4] and consists of a chamber filled with water, one end containing the piezo-electric crystal (quartz). The other end is closed by a sheet of condom rubber. The distance between the crystal and the rubber membrane is 2 cm. in the instrument used in the studies to be described. The echoscope is handled in a manner analogous to a stethoscope, the wetted rubber membrane being applied to the skin. The crystal is 0.008 inches thick and has a working face of 9 mm. in diameter.

The relationship of the electronic units comprising the machine is shown in Figure 3. An electronic clock (1) times the bursts of sound energy and starts the trace of the electron beam on the fluorescent face of the cathode ray oscilloscope tube. The sound transmitter (2), upon receipt of the pulses from the electronic clock (1), creates the electrical energy necessary to cause the piezo-electric crystal (3) to produce sound energy for the period of the pulses. The sound pulses leave the crystal in a narrow beam and penetrate the tissues. Echoes returning from the tissues are received by the same crystal between the transmitted pulses, are amplified by unit (4), and are caused to deflect the trace as shown. The process is continuously repeated and is carried on at such a rate as to give a stable trace which can be seen and photographed to produce echograms.

The machine has been described in more detail.[18]

Method of Control

Operation of the system is complicated, involving not only the electronic complex but also the effects of tissues, which are heterogeneous when related to wave length (approximately 0.1 mm.), upon sound energy. Because of the possible number of variables, biologic control was used exclusively in the series presented. As more exact knowledge becomes available from fundamental work, it is expected to be able to apply other methods of control. In each case the echograms of the lesion and of the normal tissue of origin were recorded with the echoscope positioned in exactly the same manner and without change of machine setting. In most of the cases the opposite breast was used for control. In cases 5 and 9, adjoining normal subcutaneous tissue and the opposite axilla were recorded respectively as controls.

Clinical Results

A series was made up of 19 consecutive cases of breast tumors as admitted to the hospital for treatment. The original 2 cases[1] were included, bringing the total to 21.

Method of Echographic Examination

Adjustments of the echographic machine, including gain, were made on the basis of experience. The echoscope was applied to the tissues under examination (Fig. 2). No change was made in the controls of the machine between the echogram of the lesion and the echogram of the normal tissue of origin in order to insure control of the experiments. Thus, echograms of the normal tissue of origin could be compared. The method of control makes a comparison from case to case possible only on the basis of observed differences between the echogram of the lesion and the control echogram of the same case. It is not valid to compare individual echograms from case to case.

Subjective Interpretation of Records

It has been found from previous studies that certain definite characteristics appear to distinguish echograms believed, at the present stage, to be associated with malignant tissue from the control echograms obtained from the tissue of origin. These characteristics can be distinguished subjectively on the oscilloscope screen and a probable diagnosis can be made at the time of examination. The subjective basis of interpretation of the records is explained later.

It is necessary to state the axes of the uni-dimensional echograms. Figure 4 shows a typical pair of uni-dimensional echograms from case 2. The time base runs horizontally from left to right. From this base

the depth in the tissues from which the echoes are returning can be computed. The total distance across the record corresponds to about 2 cm. of penetration into the tissues. (Each horizontal scale division is 3.0 micro-seconds and represents a distance of 2.30 mm., taking the average velocity of sound in tissues at 1540 meters per second.) The height from the baseline in the vertical axis indicates the strength or loudness of the echoes returning from the tissue.

The saturated signal "X" should be noted. This signal indicates that the echoes returning from the rubber-membrane-body-surface interface, or the point of entrance of the sound into the tissues, are so strong that

TABLE I

A Composite of the Clinical Data, the Results of the Subjective and Objective Evaluation of the Echogram Pairs in Each Case, and the Microscopic Diagnosis Made after Echographic Examination

Case no.	Hospital no.	Age	Lesion	No. of echoes†	Area†	Baseline†	Diagnosis	
							Echographic	Pathologist
				Malignant group				
1	832576	32	Whole breast	$\frac{9}{6}=1.5$	$\frac{796}{574}=1.39$	$\frac{44}{37}=1.2$	Malignant	Adeno-carcinoma
2	832585	69	Breast nodule	$\frac{11}{6}=1.8$	$\frac{508}{361}=1.40$	$\frac{48}{28}=1.7$	Malignant	Adeno-carcinoma
3	832270	38	Breast nodule	$\frac{5}{5}=1$	$\frac{580}{431}=1.35$	$\frac{28}{29}=0.1$	Malignant	Adeno-carcinoma
4	832284	55	Breast nodule	$\frac{5}{1}=5$	$\frac{698}{446}=1.57$	$\frac{42}{10}=4.2$	Malignant	Adeno-carcinoma
5	832016	66	Axillary node	$\frac{7}{5}=1.4$	$\frac{603}{507}=1.19$	$\frac{35}{32}=1.1$	Malignant	Adeno-carcinoma
6	767222	47	Breast nodule	$\frac{8}{2}=4$	$\frac{421}{329}=1.28$	$\frac{34}{12}=2.8$	Malignant	Adeno-carcinoma
7	809359	79	Breast nodule	$\frac{6}{5}=1.2$	$\frac{477}{278}=1.72$	$\frac{32}{27}=1.9$	Malignant	Adeno-carcinoma
8	661916	61	Breast nodule	$\frac{3}{4}=0.8$	$\frac{324}{247}=1.31$	$\frac{15}{13}=1.2$	Malignant	Adeno-carcinoma
9	834912	80	Subcutaneous plaque	$\frac{6}{1}=6$	$\frac{317}{298}=1.06$	$\frac{20}{8}=2.5$	Malignant	Adeno-carcinoma
10*	816988	51	Breast nodule				Malignant	Adeno-carcinoma
11	827694	87	Breast nodule	$\frac{7}{1}=7$	$\frac{426}{313}=1.36$	$\frac{30}{9}=3.3$	Malignant	Intraductal carcinoma
12	833986	51	Half breast	$\frac{10}{11}=0.9$	$\frac{739}{567}=1.30$	$\frac{54}{57}=0.9$	Malignant	Sarcoma

TABLE I (Continued)

Case no.	Hospital no.	Age	Lesion	No. of echoes†	Area†	Baseline†	Diagnosis	
							Echographic	Pathologist
Non-malignant group								
13	833951	80	Breast nodule	$\frac{2}{1}=2$	$\frac{166}{166}=1$	$\frac{13}{8}=1.6$	Non-malignant	Intraductal papillomatosis
14	680930	37	Breast nodule	$\frac{4}{5}=0.8$	$\frac{680}{697}=0.97$	$\frac{29}{33}=0.9$	Non-malignant	Fibroadenoma (pericanalicular)
15	824906	39	Breast nodule	$\frac{3}{3}=1$	$\frac{270}{338}=0.80$	$\frac{25}{20}=1.3$	Non-malignant	Fibroadenoma (intracanalicular)
16*	813490	40	Breast nodule				Non-malignant	Fibroadenoma (pericanalicular)
17	833908	33	Breast nodule	$\frac{7}{9}=0.8$	$\frac{599}{696}=0.86$	$\frac{49}{70}=0.7$	Non-malignant	Lipoma
18	833546	54	Breast nodule	$\frac{6}{6}=1$	$\frac{150}{150}=1$	$\frac{35}{35}=1$	Non-malignant	Fibrocystic disease
19	827789	56	Breast nodule	$\frac{3}{2}=1.5$	$\frac{116}{244}=0.48$	$\frac{19}{11}=1.7$	Non-malignant	Fibrocystic disease
20	827692	47	Breast nodule	$\frac{6}{4}=1.5$	$\frac{193}{177}=1.09$	$\frac{24}{20}=1.2$	Malignant	Fibrocystic disease
21	834609	42	Breast nodule	$\frac{11}{10}=1.1$	$\frac{409}{355}=1.15$	$\frac{52}{52}=1$	Malignant	Fibrocystic disease

* Original cases.

† Echographic ratios $\frac{\text{tumor}}{\text{control}}$.

the range of the machine is exceeded. The signal "X" is a convenient landmark, since subsequent signals (to the right) are coming from tissues beneath the skin.

Casual inspection of the two echograms without prior knowledge of the principles of echography reveals a definite difference between the two. The following points may be noted and compared in the subjective examination of each pair of echograms:

1. The number of echoes to the right of point "X."

2. The distance the echoes extend along the baseline to the right of point "X."

3. The character of the echoes and the distance at which they occur along the baseline, relative to the point "X."

4. The vertical height to which the echoes rise from the baseline.

When these four points are compared in the two echograms in Figure 4, it will be noted that: The echogram of the lesion "B" shows a greater number of echoes (approximately 10) than the control echogram "A" (approximately 3). The echoes in the echogram of the tumor extend along the baseline to a far greater extent than those of the control echogram. Thus the tumor was returning echoes from a greater depth than was the normal breast tissue. The closeness of the lesion to the skin, noted clinically and microscopically, can be seen in the echogram "B" at "Y" occurring with the bifid entering signal "X." Finally, the signals returned from the tumor echogram "B" are considerably higher, or stronger, than those from the normal "A." (The signal "Z" shown in the normal echograms was frequently observed in the series and is considered a normal signal from the human breast.) From experience gained in previous work, a diagnosis of a malignant neoplasm was made on the basis of the positive differences between the two echograms.

In contrast, the pair of echograms from case 15 shown in Figure 5 can be examined. Both echograms show about the same number of echoes. But the echoes in the echogram of the lesion "B" show less amplitude. Both show about the same horizontal extent. The lesion of "B" shows a somewhat smaller over-all echo pattern than does the control "A" of normal tissue. A diagnosis of benign tumor was made on this negative difference between the control and the lesion, again on the basis of hypothesis.

The echograms from case 12 (sarcoma) are shown in Figure 6. The control is shown at "A" and the lesion at "B." In this case, the number of echoes and the baseline extent were approximately the same. But a diagnosis of a probable malignant lesion was made on the basis of the group of echoes under the broken line (see point 3).

The preoperative echographic diagnoses, based on the hypothetic points of comparison between the two echograms in each case, are shown in Table I, together with relevant clinical data and the microscopic diagnoses. Cases 1 to 12 were diagnosed microscopically as malignant lesions, and cases 13 to 21 as non-malignant.

Objective Evaluation

Subjective examination of the echograms suggested three possibly significant characteristics which seemed amenable to quantitative analysis. These characteristics are: the number of echoes, the baseline extension of echoes, and the area beneath the trace (average returned sound). The numerical data for these variables are shown in Table I.

Echoes were not counted as such unless higher than baseline thickness. Baseline extension of echoes was measured in millimeters from the beginning of the entering signal "X" to the beginning of the last counted echo.

Area, which is proportional to the average energy received from the system, was computed by tracing the echo pattern from the original records, including the entering signal "X" and the last counted echo, upon paper ruled in millimeters in both directions. The difficulties of handling trace line width in connection with area determinations led us finally to accept only whole square-millimeter units as contributors to total area. Thus the areas given in Table I are minimal.

Ratios of tumor to control were determined for every case. The malignant and non-malignant groups were then compared with respect to the average values of these ratios. The "t" test of "Student" was used for the statistic evaluation of probability that the observed differences in these averages might arise purely through chance. With 17 degrees of freedom pertinent to each "t" value (1.9 for echo number, 4.9 for area, and 1.8 for baseline extension) the resultant probabilities are .071, .0002, and .09 respectively for echo number, area, and baseline extent. The only clearly significant ratio appears to be that for area where it will be noted that all cases diagnosed microscopically as malignant had a ratio above unity. The lowest area ratio in the malignant group (case 9) was 1.06 as compared to the highest area of 1.15 in the benign group (case 21). Thus overlapping of the two groups is very small.

TABLE II
Clinical Composition of Series

Malignant Neoplasms		Non-Malignant Lesions	
Adenocarcinoma in breast	8	Intraductal papillomatosis	1
Adenocarcinoma remote	2	Fibro-adenoma (pericanalicular)	2
Intraductal carcinoma	1	Fibro-adenoma (intracanalicular)	1
Sarcoma	1	Lipoma	1
		Fibrocystic disease with fat necrosis	2
		Fibrocystic disease without fat necrosis.	2
Total	12	Total	9

Table II shows the composition of the series based on microscopic structure.

TWO-DIMENSIONAL ECHOGRAMS

The adenocarcinomas showed the usual variation of cellular and fibrous components from section to section, but the differences between the uni-dimensional echograms of case 6 (Fig. 7) were not as striking subjectively as the other cases. Since at this time, pilot apparatus for

two-dimensional echography had come to hand, the opportunity arose to try to obtain more evidence in this case. Figure 8 shows the results of the attempt, and is believed to be the first record of its kind taken from the human breast. The principles of two-dimensional echography have been fully described elsewhere.[12] The deeper echo pattern of the lesion "B" can be readily seen. (The time axis is from below upward.) The records are of small sectors of tissue in one plane.

With development of the apparatus it is hoped to draw a picture in terms of echo pattern which will define a tumor directly, thus greatly facilitating interpretation. The tumor in this case was too large for the available range of the instrument.

The area of control echograms "A" (Fig. 8) (on the original records) was 580 square mm. and that of the tumor "B" (Fig. 8) 1121 square mm., giving a ratio of 1.93.

It was interesting to note that, although the subjective interpretation of the uni-dimensional echograms of case 6 revealed only a moderate difference between the two records (Fig. 7, A and B) as compared to the other cases of which Figure 2 is typical, the objective evidence obtained from both the uni-dimensional and the two-dimensional echograms indicated a malignant tumor.

Case Discussion

The secondary deposits in regional lymph nodes (case 5) and in the subcutaneous tissues (case 9) gave similar patterns to those of lesions within the breast on other cases. Case 9 also exhibited massive involvement of the thyroid gland, which gave the same pattern of echoes as the subcutaneous plaques, though control from the thyroid gland itself was not possible.

Case 8 was recorded as doubtful subjectively because of only a moderate difference of echo pattern in one of three records (the other two being conclusive). The pathologist reported the lesion as well circumscribed, necrotic in parts, and that the histologic diagnosis was less clear-cut than for the rest of the cases, and that "there was room for an honest difference of opinion." However, the area ratio of the doubtful echogram fell into the malignant range.

Case 11 (Paget's disease) gave quantitative data indicating a malignant lesion whereas case 13 (intraductal papillomatosis) fell into the "normal" (area ratio) quantitative zone. Cases 13, 20, and 21 were subjectively designated as malignant in the interest of the patients, but case 13 did not warrant this designation on the basis of the quantitative analysis.

In the quantitative study, the ratio of areas under the echograms appears to be a significant entity agreeing completely with the microscopic diagnosis in the malignant group.

Consideration of Production of Echoes by Tissues

From the beginning, echographic studies on effects of tissues in terms of cells have been hampered by the absence of precedent, so that approach has of necessity been experimental. As experimental data have become available, it has been possible to attempt application of the theory of sound. Most of the exact knowledge of sound is predicated upon homogeneous mediums. At a frequency of 15 megacycles, the present upper practical limit of echographic application, the wave length is about 0.1 mm., or 100 μ, so that if a cell diameter is assumed at 10 μ, the theoretic limit of resolution at 15 megacycles could be about ten cells. Unfortunately, tissues must be considered not only as heterogeneous on a possible scale of ten-cell units, but also extremely complex geometrically, so that a theoretic approach to the problem becomes overwhelmingly difficult at 15 megacycles. It is possible, however, once this fact is appreciated, to apply some of the known theory cautiously and to devise experiments with at least some of the variables controlled. Fundamental work is in progress designed to elucidate some of the observed phenomena in relation to the problem.

The difficulties of the purely theoretic approach and the necessity for clear biologic thinking become apparent when attempts are made to obtain physical constants from biologic tissues. Ludwig,[14] measuring velocity of sound in isolated tissues at 1.25 to 2.5 megacycles by a transmission technic, found a variation of 1506 to 1585 meters per second in brain, liver, kidney, spleen of dog, and hog and beef muscle. In the living subject for various groups of muscles in several individuals the range was from 1490 to 1610 meters per second.

Ludwig[14] found that within the limits of experimental error the velocity of sound did not differ significantly when the sound energy traversed the tissue parallel to the muscle bundles or across them. Hüter,[15] using a transmission technic, measured the absorption of sound by similar blocks of tissue. He found that the absorption of sound was greater when the sound energy was directed across muscle bundles than when directed along the muscle bundles.

We have helped to explain this effect of anisotropy (fiber direction) of beef muscle by the echographic technic used in this communication. We have found that sound is reflected back toward the source in the

crosswise direction and practically not at all along the fibers. Thus the natural orientation of beef muscle presents interfaces at which sound can be absorbed or reflected when the sound energy is directed normally to the plane of the fibers (across). We found echographically that the orientation was destroyed by grinding the meat.

We have noticed also a marked difference of echo pattern with and without intact blood supply.

The echographic method of examination will make possible more exact measurement in terms of small units of tissue in the future, but in the meantime advance can be made with empirical procedures such as the study described.

Our hypothesis relative to the present study is based upon the greater concentration of nuclear material found mainly in malignant growths, since we may be differentiating groups of ten cells theoretically. The evidence for this hypothesis is based partly on the fact that necrotic malignant tissue apparently does not return echoes as compared to a living cell mass. If this fact is true, the one doubtful subjective verdict (of three echograms) in the malignant group (case 8) might be explained.

It should be appreciated that the present apparatus is extremely crude when compared to possible future development. Echography appears to be applicable to all accessible sites of tumor growth.

Summary

An echographic study was made of 21 cases of tumors associated with the human breast (Table II). Control was biologic throughout the series. The cases were examined as presenting in the clinic for preoperative diagnosis. An echographic diagnosis based on hypothesis was made before operation (Table I), and compared with the subsequent microscopic diagnosis.

The original records were subjected to quantitative analysis. The quantitative echographic diagnosis based on the records obtained appeared to agree completely with the microscopic diagnosis in the malignant group on the basis of a statistically significant entity, the area (average returned sound) ratio.

Differentiation between intraductal papillomatosis (case 13) and intraductal carcinoma (case 11) was possible. Some typical records illustrate the discussion.

Two-dimensional echograms of the human breast (Fig. 8) are believed to be the first recorded.

The patients examined did not complain of, or admit, any sensa-

tions when examined. The pathologist did not comment upon any unusual appearances of the specimens when examined. The operators of the machine have not experienced any untoward effects to date (7 months). No precautions were taken by the operators.

Echography appears to be applicable to tumors at all accessible sites. Further inquiry along the lines described would seem justified.

We are indebted to Norman Jacob, M.D., Department of Pathology, University of Minnesota, and Clinical Fellow, American Cancer Society, for his checking of the pathology sections of this paper and his constant helpful suggestions during the progress of the work in which he was actively interested in his capacity as hospital surgical pathologist; to A. E. Treloar, Professor of Biostatistics, School of Public Health, University of Minnesota, for his kind help on the biostatistical evaluation of the objective results; and to Maurice B. Visscher, Professor and Head, Department of Physiology, University of Minnesota, and Henry E. Hartig, Professor and Head, Department of Electrical Engineering, University of Minnesota, for their kind help and suggestions in the preparation of this paper.

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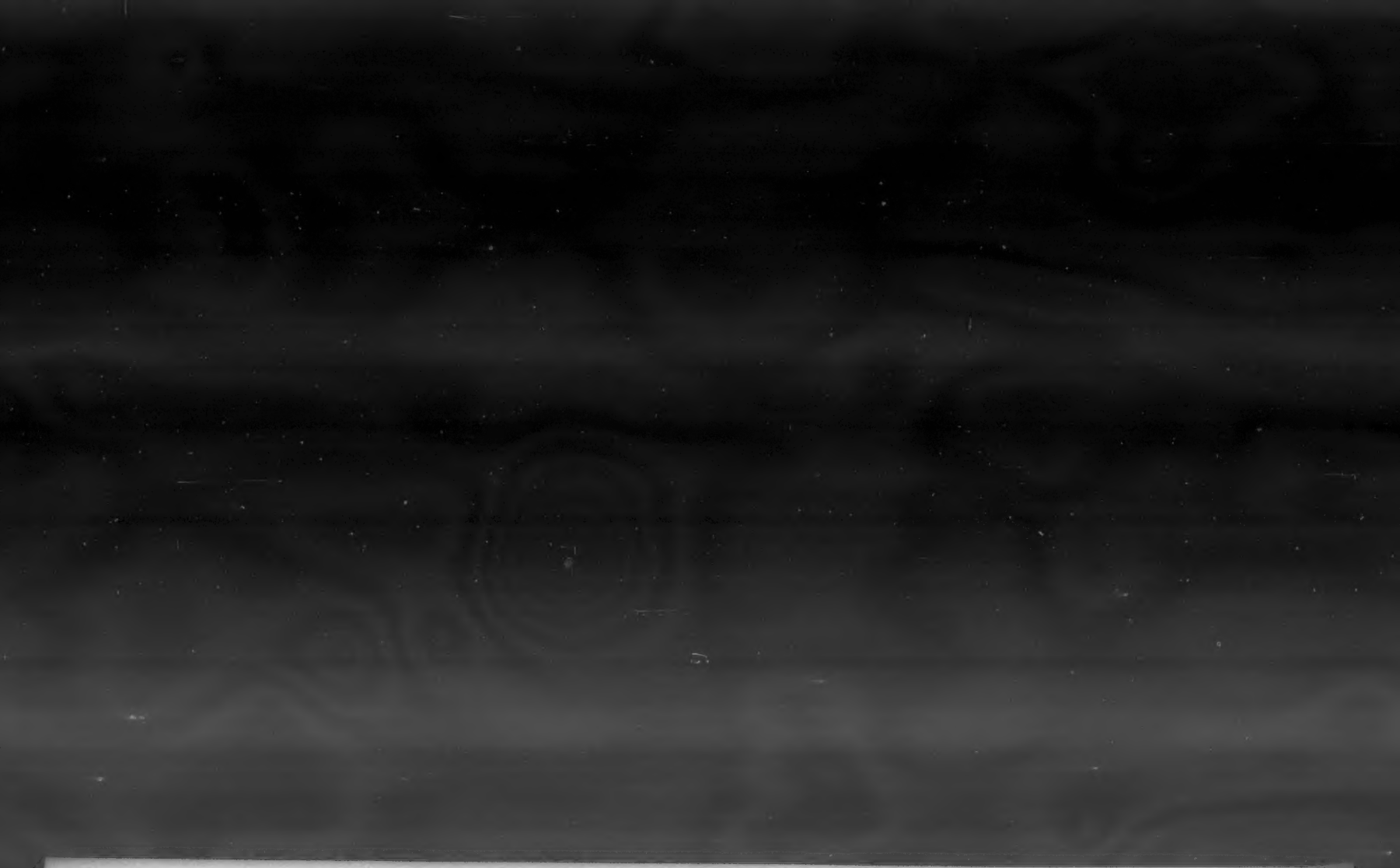
DESCRIPTION OF PLATES

PLATE 129

FIG. 1. The 15 megacycle echograph arranged for clinical work. The power supply unit is to the left and the transmitter, receiver, and control units to the right of the substage. The echoscope is seen on the table top, clamped to a stand. The camera is shown in position for recording. It can be swung clear for detailed examination of the oscilloscope. The boiled distilled water used for filling the echoscope is shown stored under oil in the bottle between the clamp stand and the oscilloscope.

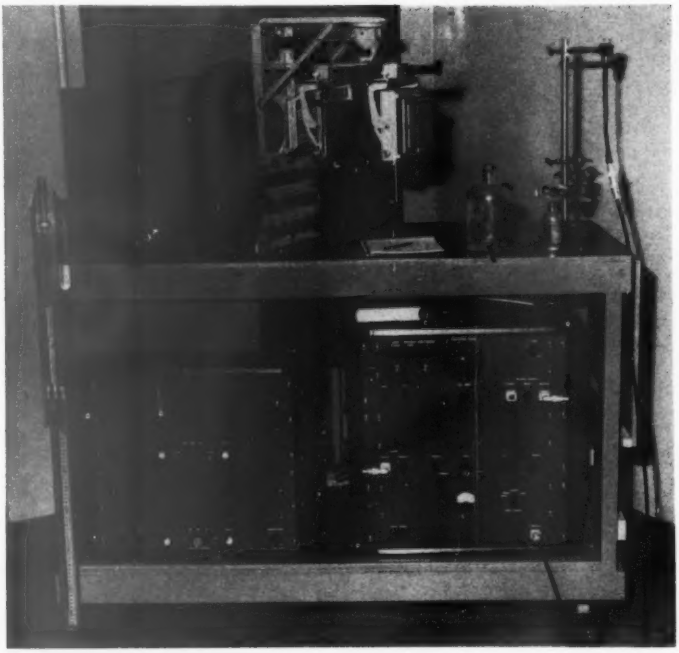
FIG. 2. Method of examination of the patient. The echoscope is shown applied to a lesion of the right breast.



AM

W

1



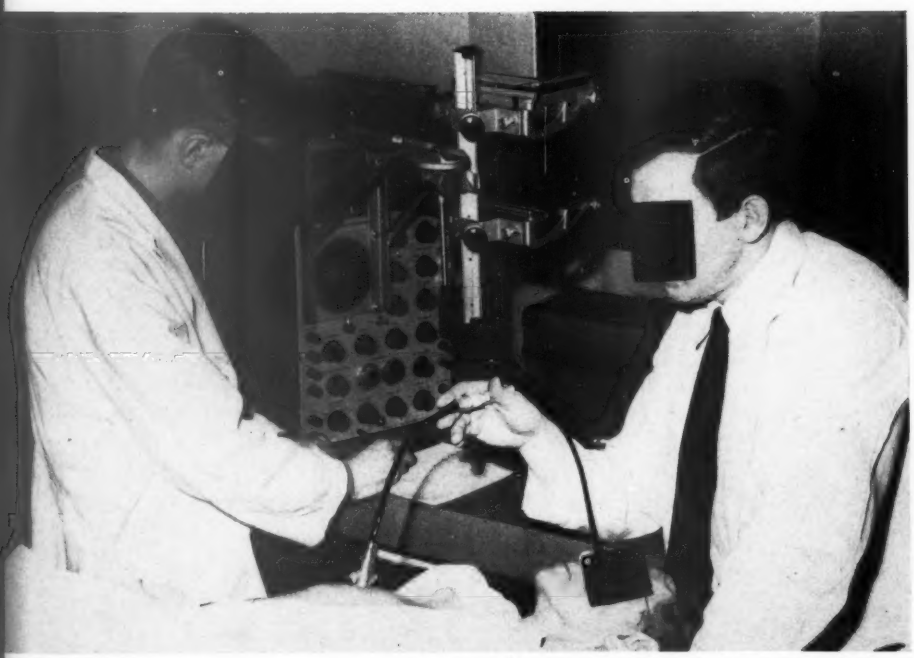
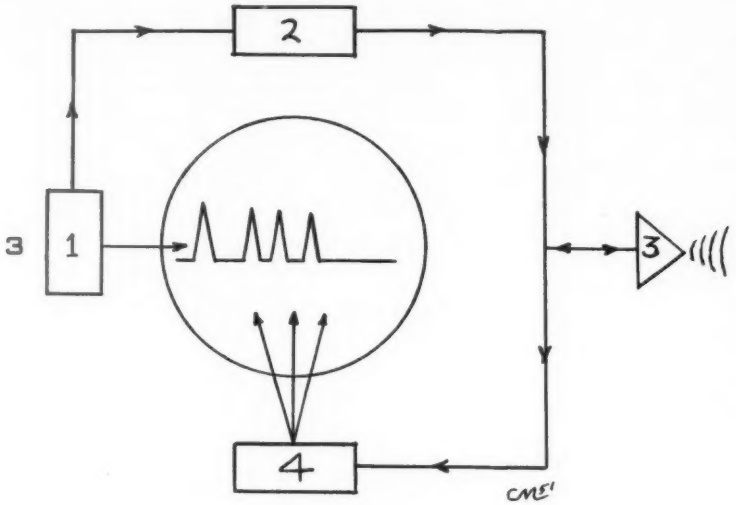


PLATE 130

FIG. 3. A schematic diagram of the apparatus. The electronic "clock" (1) starts the trace on the oscilloscope and times the bursts of sound energy produced by (2) into the piezo-electric crystal (3). Returning signals pass to amplifier (4), and are recorded continuously on the oscilloscope as shown.

FIG. 4. A typical pair of echograms obtained from a malignant lesion (case 2, adenocarcinoma). The control echogram ("A") is from normal breast tissue. The entering point of the sound into the tissues is designated "X." (The echo "Z" was frequently seen in the normal breast.) The echogram of the lesion ("B") demonstrates the greater number and strength of the echoes arising deeper in the lesion. The interpretation is described in the text. (Time base 3.0 microsecs. per division horizontally.)


2
3
1
3
4
CME'

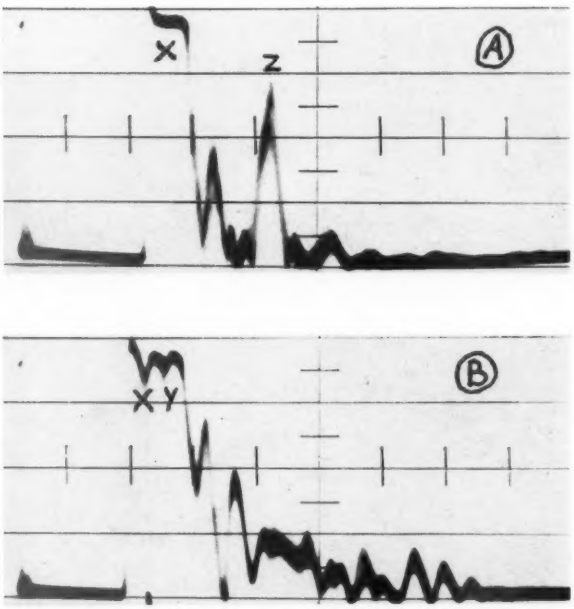
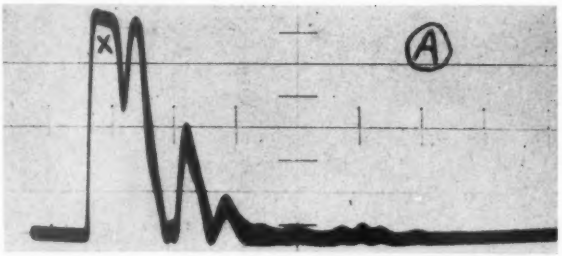

X
Z
A
4
X Y
B

PLATE 131

FIG. 5. A pair of echograms of a benign lesion (case 15, fibro-adenoma). The normal echogram "A" shows a slightly fuller echo pattern than does the lesion "B." (Time base 3.0 microsecs. per division horizontally.)

FIG. 6. A pair of echograms from case 12 (sarcoma). The normal ("A") should be compared with the lesion ("B"). The greater strength of the echoes arising deep in the lesion is demonstrated under the broken line. (Time base 3.0 microsecs. per division horizontally.)



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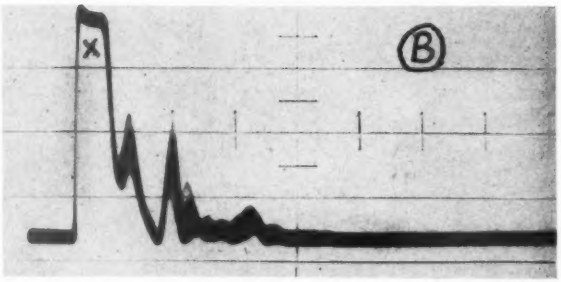

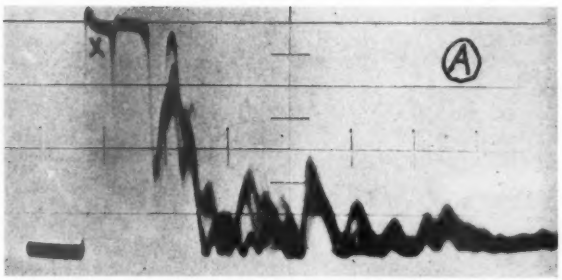

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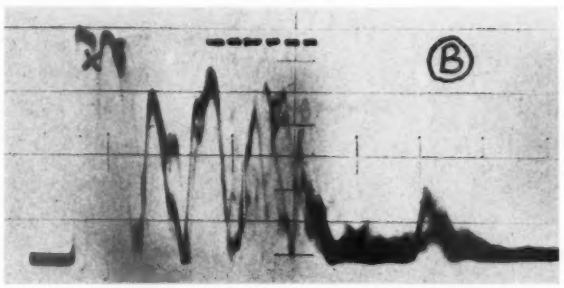
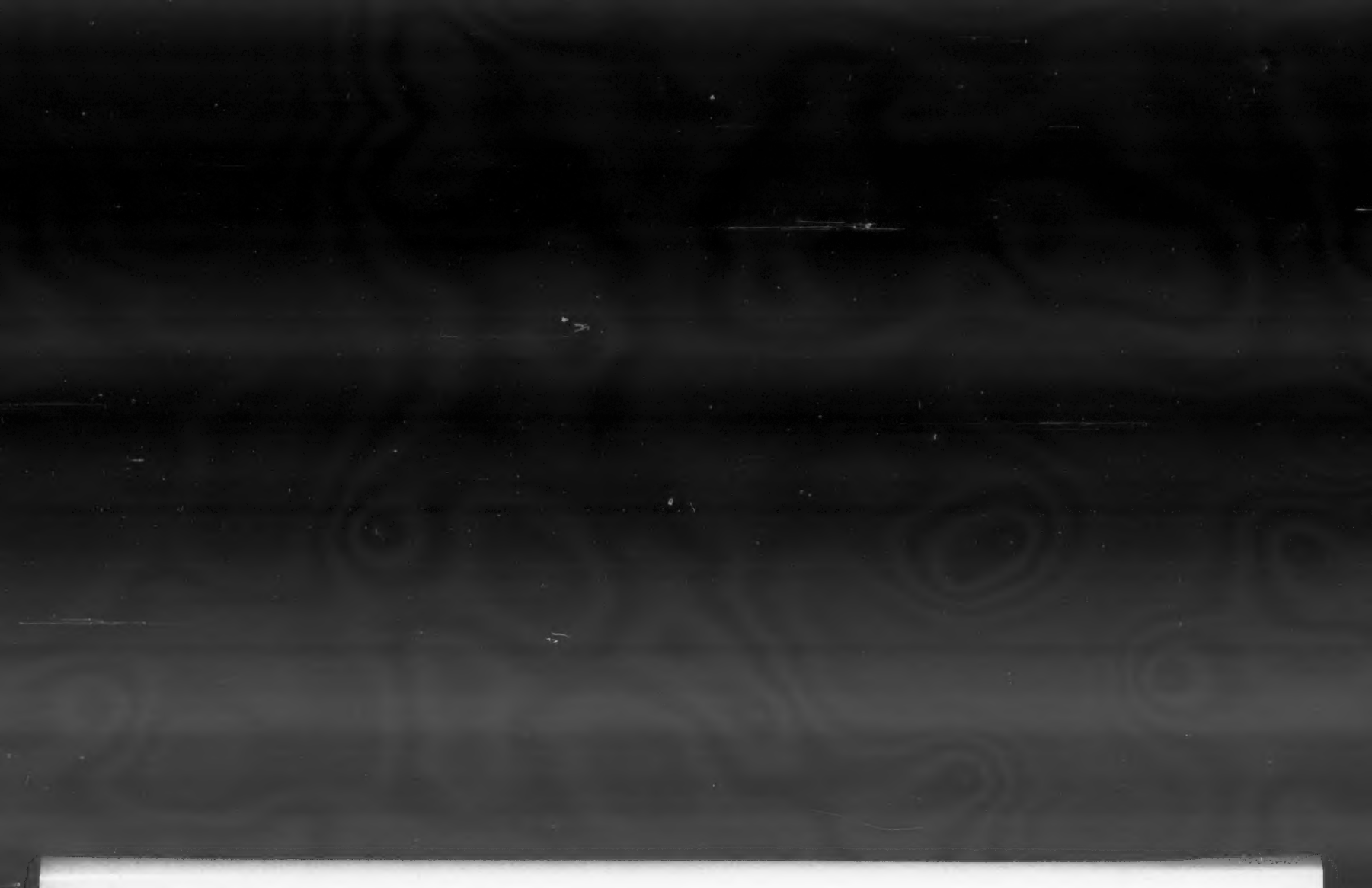
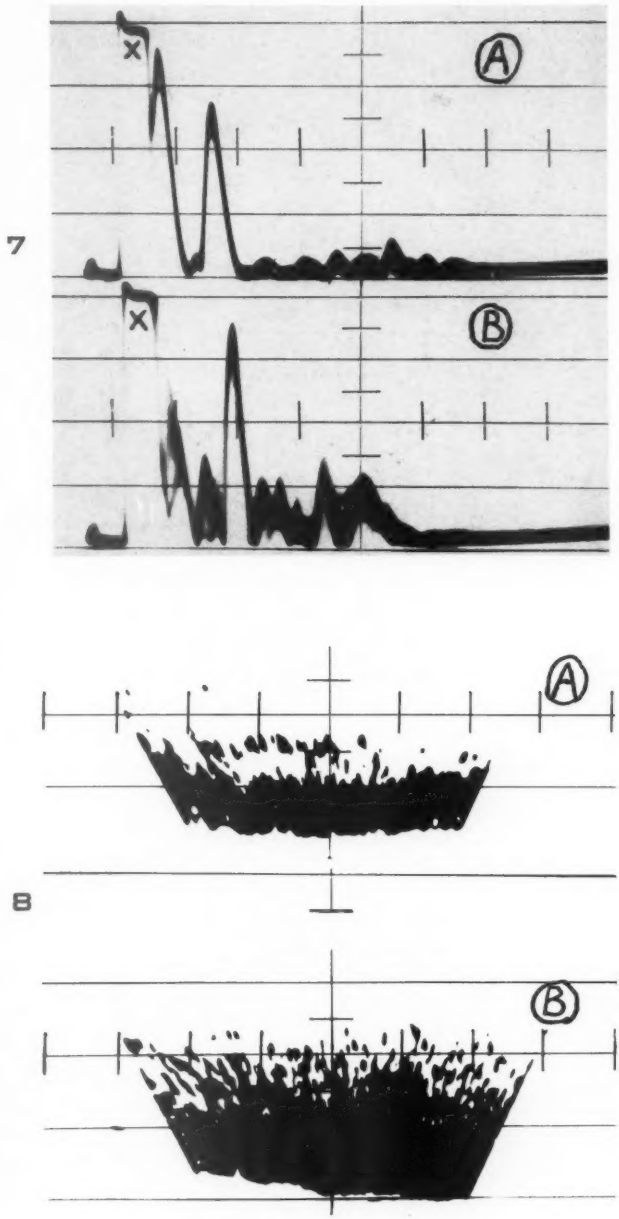


PLATE 132

FIG. 7. An apparently less marked difference in the uni-dimensional echograms from case 6 for comparison with Figures 4 and 8. (Time base 3.0 microsecs. per division horizontally.)

FIG. 8. The two-dimensional echograms of case 6. The *difference* between the normal ("A") and the lesion ("B") should be compared with the difference in Figure 7. (Time base vertical.)




7
X
A
X
B
8
A
B

FROZEN SECTIONING
A New and Rapid Method *

Vannevar Bush and Richard E. Hewitt
(From the Carnegie Institution of Washington, Washington 5, D.C.)

This paper describes a new method of making sections of frozen tissue on the microtome. The process is simple and time saving. It can be used to advantage for normal diagnostic purposes. With it, undistorted thin sections can be cut from fragile tissues such as fatty tumors, thyroid glands, and lymph nodes.

Methods now in general use are usually satisfactory for rapid diagnostic work when practiced by highly skilled pathologists. The manipulative skill necessary is considerable, however, and a simpler and more dependable process should be welcome, to handle the large amount of material now being examined. Furthermore, some tissues are so fragile that undistorted thin sections are very difficult or even impossible to obtain by present methods.

In current methods the sections are cut off and then mounted. In the new method the sections are mounted and then cut.

The essential feature of this improved technic is the furnishing of support to the tissue during the slicing stroke. This is accomplished by sticking a thin film to the freshly cut surface of the frozen specimen block and then cutting the section while it adheres to and is supported by the film. A similar principle was successfully employed in an automatic microtome for making biologic sections of paraffin-impregnated specimens, as described in a separate paper.[1]

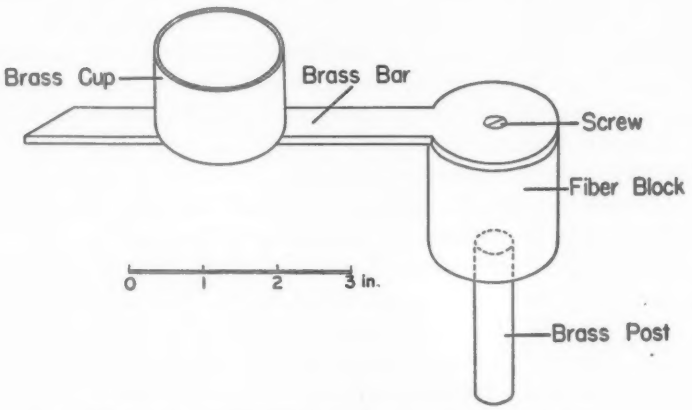
The process is facilitated by a reliable means of temperature control for the specimen and knife. For this purpose the arrangement shown in Text-figure 1 was developed. The plate on which the specimen is mounted is supplied with a metal arm on which a brass cup is clamped in the position desired. When the cup is filled with solid CO_2 (dry ice), temperature equilibrium is rapidly attained. The temperature of the specimen may then be adjusted by moving the cup in or out on the arm. Once a satisfactory setting is obtained, it may be kept unchanged with subsequent specimens as long as room conditions remain essentially unaltered. A similar cup arrangement may be used to cool the knife. The standard freezing attachment may be modified for the use of carbon dioxide gas.

In the usual method of sectioning, the top of the specimen block is brought to a semi-congealed condition in order to avoid having the

* Received for publication, June 28, 1952.

section crumple as it is cut. With the new method the section remains securely frozen. The temperature of the block is not highly critical. About −15° C. has proved satisfactory. If it is much lower than this, trouble may be experienced in making the film adhere to the block, as will be described. The temperature of the knife should be low enough so that it does not cause fusion of the section as it slices.

To secure adhesion, the following method has been developed. A strip of film base is coated with a thin layer of soft gelatine. The gelatine is softened in water and the surface moisture sponged off. When



Text-figure 1. Temperature control for the specimen and knife.

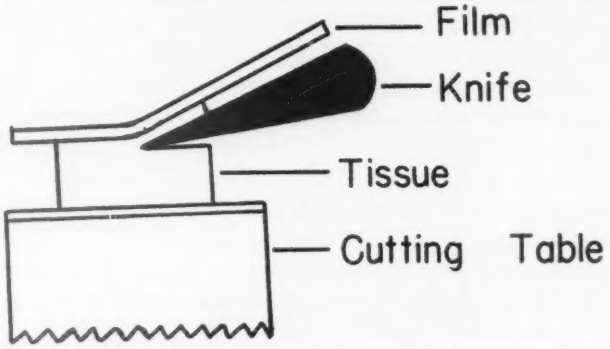
the coated film is pressed down on the freshly cut surface of the block, it will freeze to it and adhere strongly. For this to occur, temperatures should be such that, when the film is pressed on with a tool of low thermal conductivity, there will be incipient fusion of the top of the block followed by prompt freezing. It appears that this incipient fusion extends only a very few microns into the block.

A cellulose film* base 15 or 24 μ thick, coated with soft gelatine 10 μ thick, has been found satisfactory for the adhesive process. This film was supplied mounted, as a stripping film, on a relatively heavy cellulose acetate base for convenience in handling. The gelatine-coated film is peeled off just before using. All commercially available photographic film is on too thick a base, or has too hard a gelatine for the purpose. Eastman Kodalith Thin Base Film, however, can be used successfully for some purposes if given an additional thin overcoat of

* The Eastman Kodak Company has kindly provided a special film from its laboratories. They have agreed to supply limited quantities of experimental material for research, and the Industrial Photographic Sales Division should be addressed if film is desired.

soft gelatine. Slight hardening of the gelatine in alum is desirable, but the gelatine should be kept soft enough to swell readily in a few seconds in water at room temperature. A base material thicker than 25 μ is more convenient to handle, but is not so well adapted to very thin sections.

After the film has been made to adhere to the specimen block, the edge of the film is lifted with thumb forceps and raised gently as the knife is passed through the specimen beneath. Text-figure 2 shows the



Text-figure 2. Relations of film, knife, tissue, and cutting table.

relations, of course with exaggerated dimensions. With the film described, sections 5 μ thick are readily obtained.

The film with section adhering is laid face up on a slide, where the section will promptly thaw. It can then be stained by any usual method and a coverglass added. One precaution should be noted: the staining should be delayed briefly. When the section fuses, a thin layer of water passes between it and the gelatine, owing to capillarity. If staining is delayed a minute or two, this water evaporates or is absorbed by the gelatine, whereupon the section adheres well. The evaporation process is facilitated if the soaking of the gelatine is brief, so that not much water will have been absorbed before the staining is begun. The usual hematoxylin and eosin staining gives satisfactory results.

A new and more convenient method of staining is as follows: The gelatine film itself is pre-stained. It can then be used immediately or dried and stored for later use. The film is used as before and placed on a slide with its adhering section. It is immediately ready for diagnosis. If a more stable section is desired, the coverglass is added immediately, preferably with an aqueous mounting medium. By the time the slide is taken to the microscope it will be found that the stain has transferred from the gelatine to the section. By controlling the

staining of the gelatine and the acidity, uniform results are obtained. This modified method of staining is rapid; a finished slide can be made from a frozen specimen in about a minute. The skill necessary is readily learned.

The pre-stained gelatine method has operated well with an aqueous solution of thionine or of toluidine blue. Sometimes it is desirable to add a small amount of eosin. But satisfactory metachromatic staining can be secured with toluidine blue diluted 1 to 500 with pH 3.2, as may be seen more clearly in Figures 3 to 6.

The photomicrographs reproduced in Figures 1 to 6 show tissues that have appeared difficult to handle in the past.

This method of sectioning frozen tissue is so new that possible variations have by no means been completely explored, and it is hoped that publication of this paper will stimulate such exploration. In particular, vacuum desiccation of the frozen cut sections should be tried, since desiccation will then be rapid. A few tentative comments may be added from our experience to date.

Apparently very little damage is done to tissue when it is frozen rapidly or thawed rapidly. This conclusion is indicated by the classic work on materials desiccated in vacuum.[2-4] Damage does occur if tissue is held just below 0° C. for an interval, presumably because ice forms in cells, leaving relatively concentrated solutions to produce high osmotic pressures. With semi-congealed material distortion also occurs because of friction on the knife edge in the presence of remaining fluids. Added difficulty often results when frozen sections are cut by current methods, since a fully frozen specimen will crumble under the knife. The new method, which avoids these difficulties, should therefore give improved results. With specimens promptly frozen to avoid autolysis, it appears that results favorably comparable to those attained with paraffin impregnation are attainable.

The new method can be used with fresh specimens, or with specimens fixed in formaldehyde. For prompt diagnostic purposes use of fresh specimens is preferable because it saves time and avoids the shrinkage that results from fixing. A fixative may be included with the mounting medium if relative permanence is desired. Large sections can be cut from 5 to 10 μ thick as easily as small sections.

The transfer method of staining operates with surprising speed. It is difficult to get a freshly prepared slide under the microscope quickly enough to observe the transfer. A little experience with the time during which the gelatine is immersed in the staining solution and with the temperature and acidity of the stain will soon ensure a satisfactory intensity. If these conditions are right, the stain in the vicinity of the

section will pass out of the gelatine completely, leaving it colorless. When suitable staining conditions have been determined, results will be uniform on a given tissue.

The transfer method of staining appears to have other applications. Preliminary tests have been carried out on smears made directly on a sheet of stained gelatine, depending on transfer for staining. This method may be useful for cytologists when the number of cells is small and ordinary staining processes are correspondingly difficult.

As this research has extended far afield from the authors' normal experience, the advice of those familiar with the subject of sectioning has been especially necessary and appreciated. Dr. George W. Bartelmez, consultant at the Institution's Department of Embryology, from his long mastery of the subject has been helpful. We are especially indebted to Dr. William R. Duryee, cytologist, National Cancer Institute; Dr. Theodore Winship, pathologist, Garfield Memorial Hospital; Dr. Thomas Bradley, Washington, D.C.; and Dr. R. D. Bush, assistant in surgery, Boston University School of Medicine, Boston, Massachusetts, for specimens, criticisms, and suggestions.

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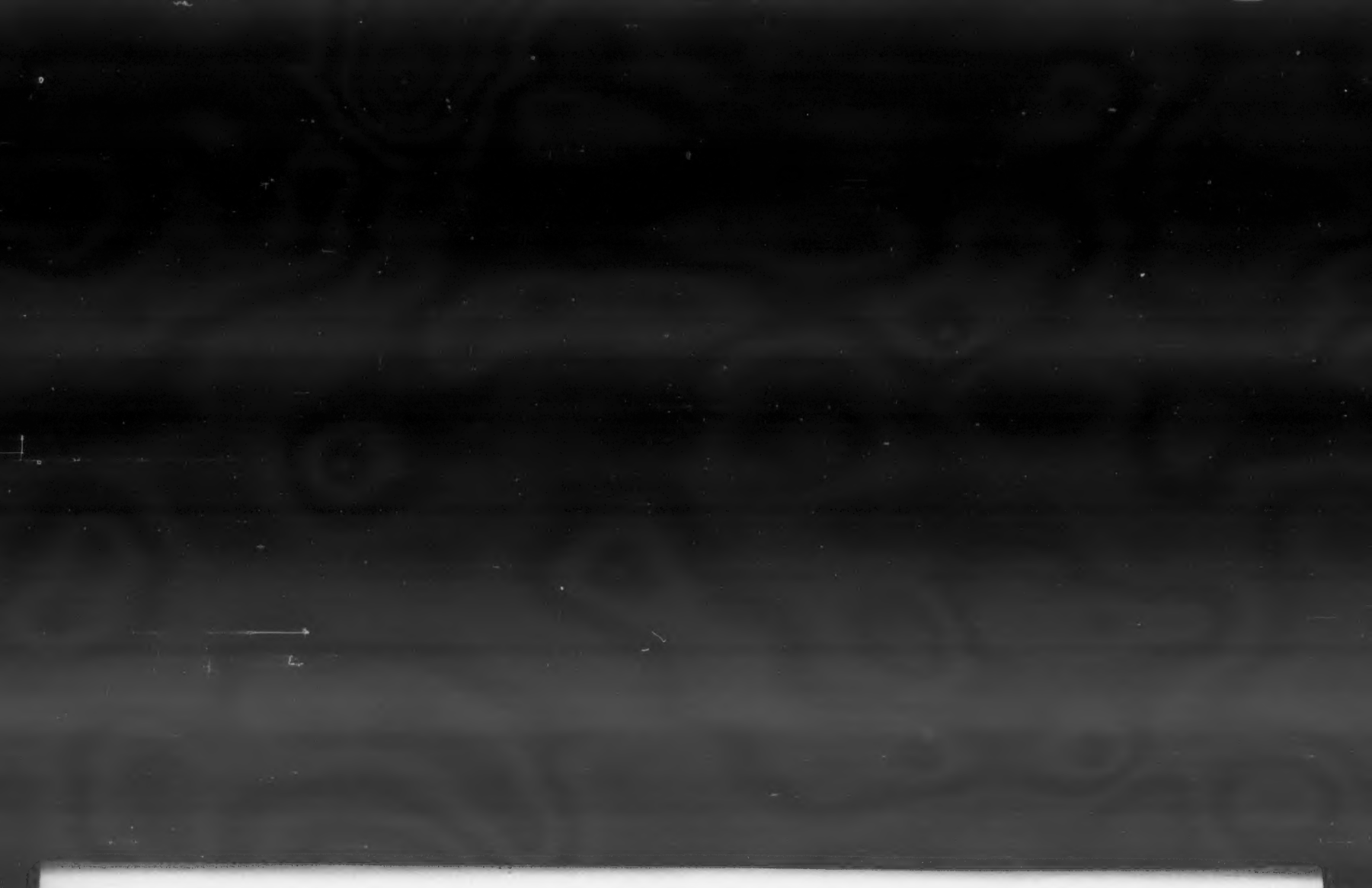
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 133

FIG. 1. Lung tissue cut at 5 μ, showing edema secondary to cardiac failure. Toluidine blue O stain. $\times$ 75.

FIG. 2. Adenocarcinoma of the rectum showing invasion of the wall. Formalinized tissue was cut at 10 μ. Toluidine blue O stain. $\times$ 75.



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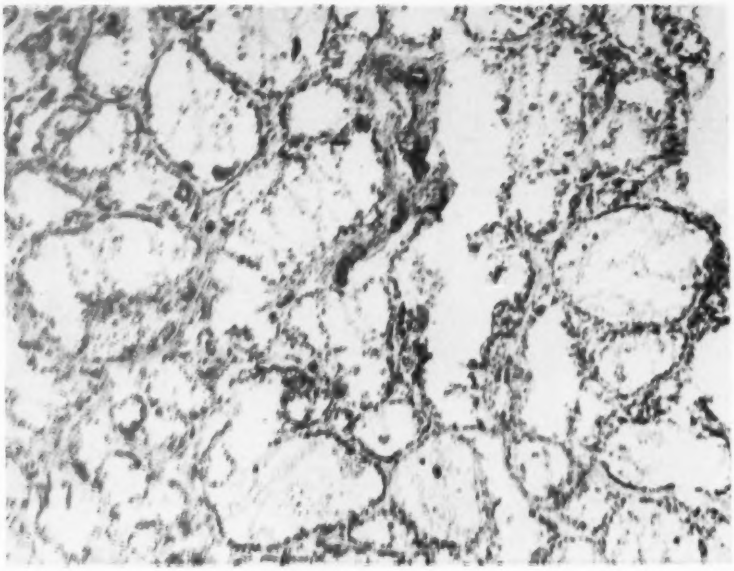

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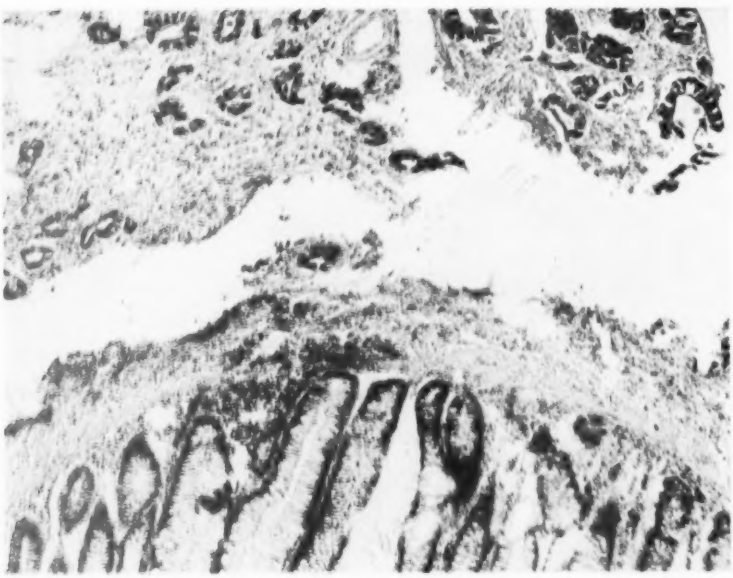
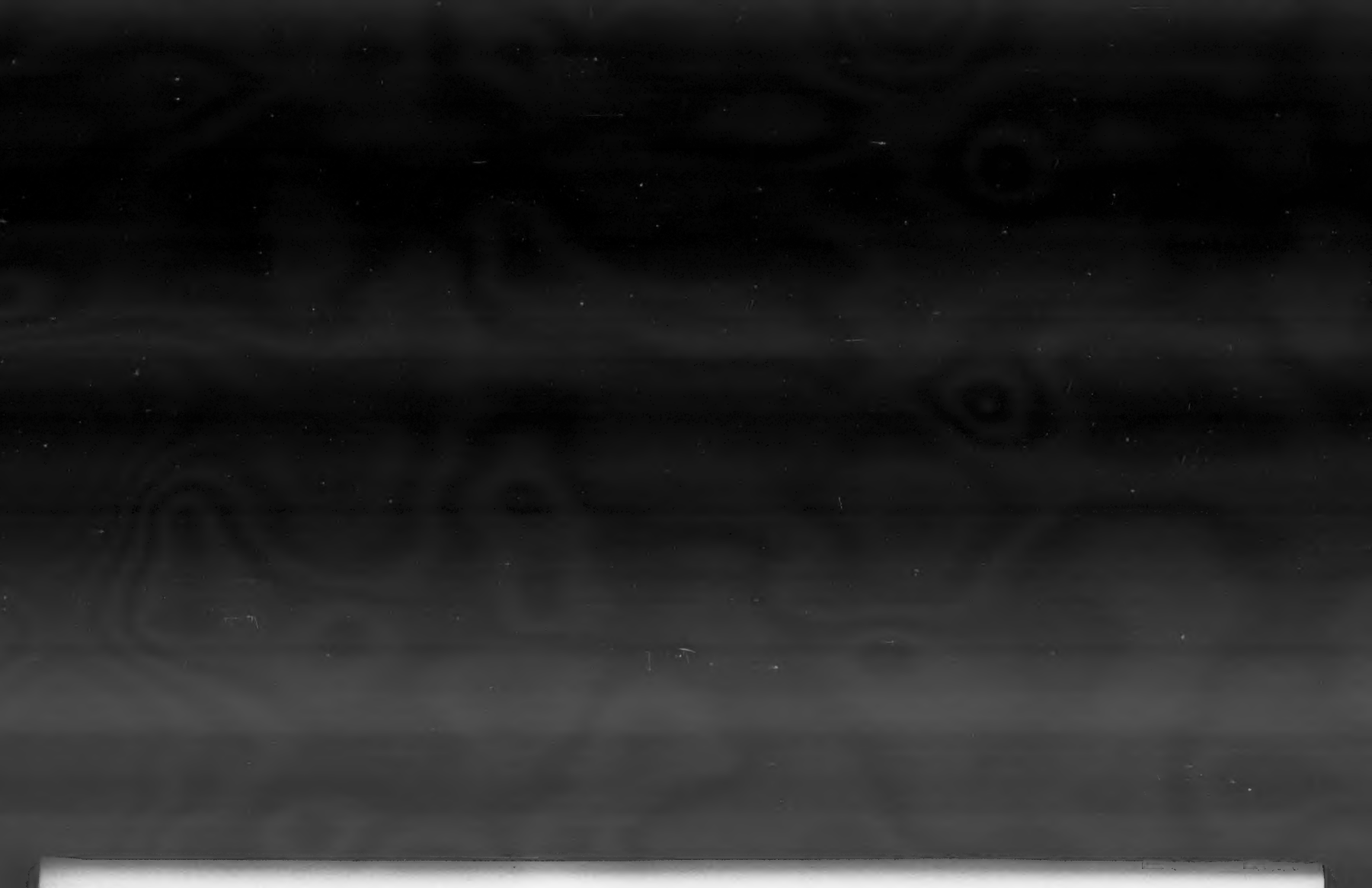


Bush and Hewitt Frozen Sectioning

PLATE 134

FIG. 3. Normal colon cut at 10 μ. Formalinized tissue. Toluidine blue O stain. $\times$ about 225.

FIG. 4. Fatty tissue cut at 5 μ showing the normal shape of the individual fat cells. Toluidine blue O stain. $\times$ 120.



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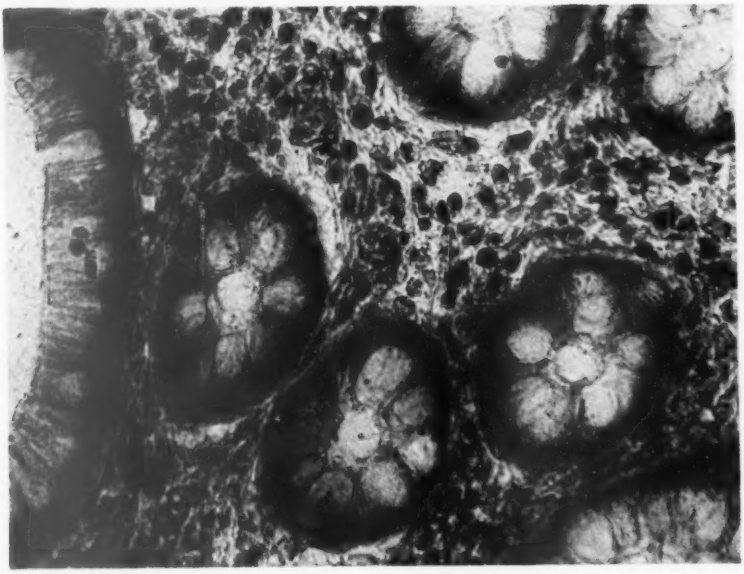

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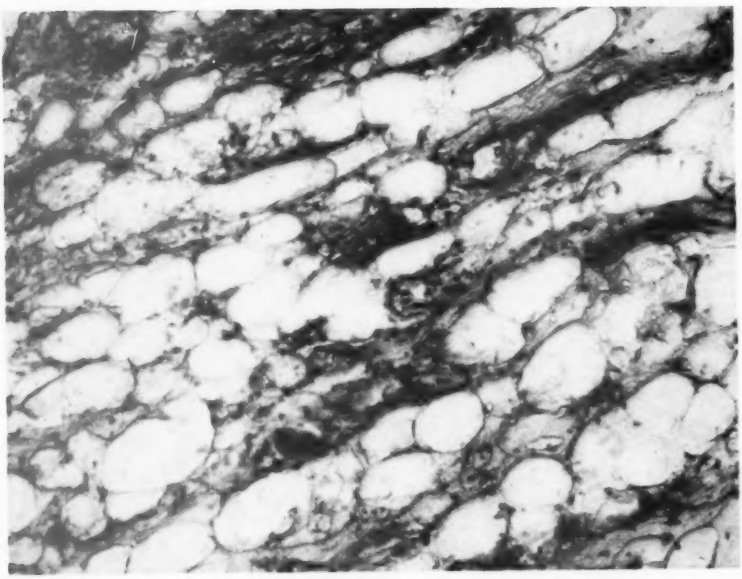
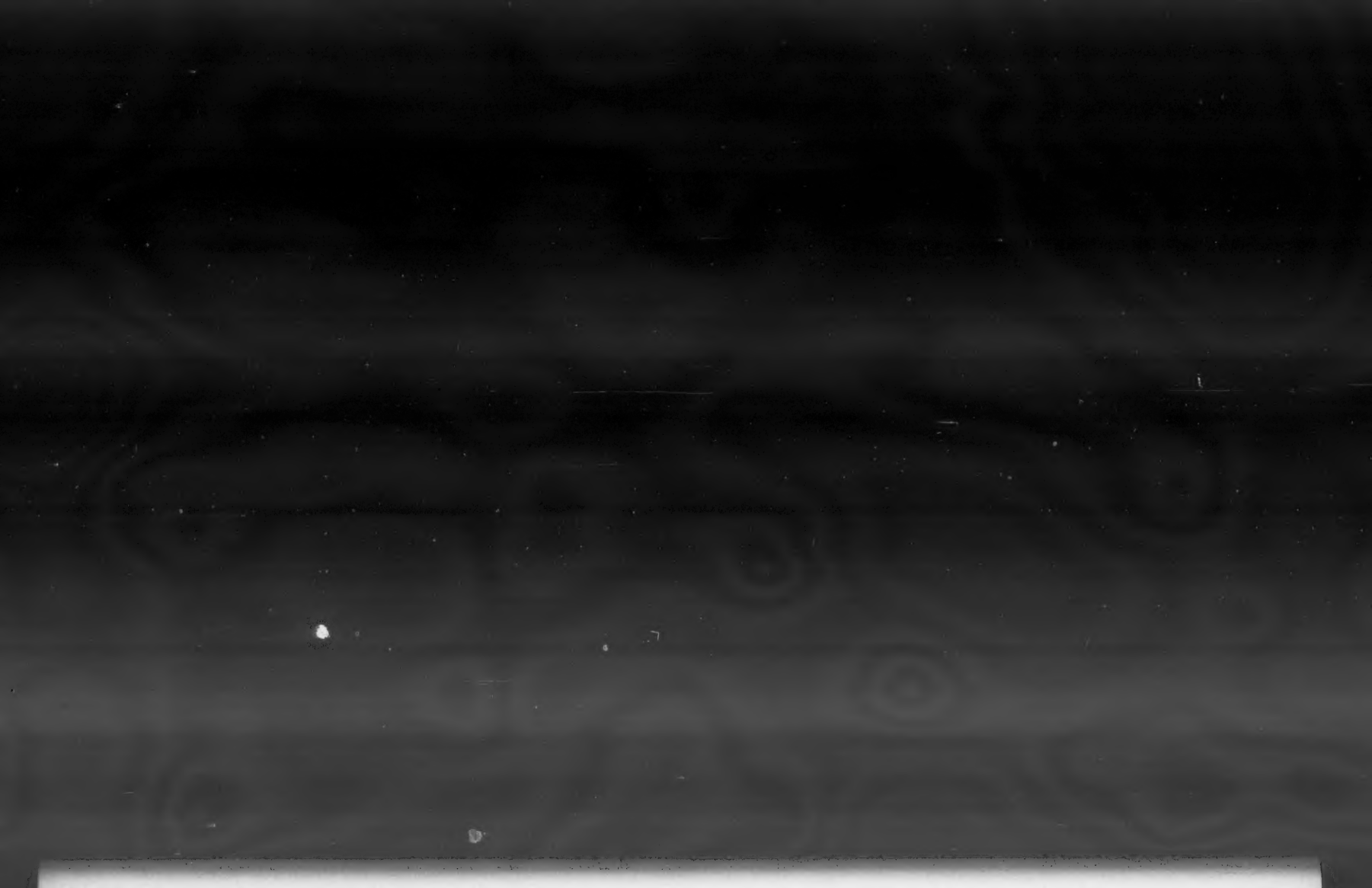


Bush and Hewitt Frozen Sectioning

PLATE 135

FIG. 5. Bronchogenic squamous cell carcinoma cut at 5 μ. Toluidine blue O stain. $\times$ 85.

FIG. 6. Breast tissue cut at 10 μ showing lobular hyperplasia. Toluidine blue O stain. $\times$ 100.



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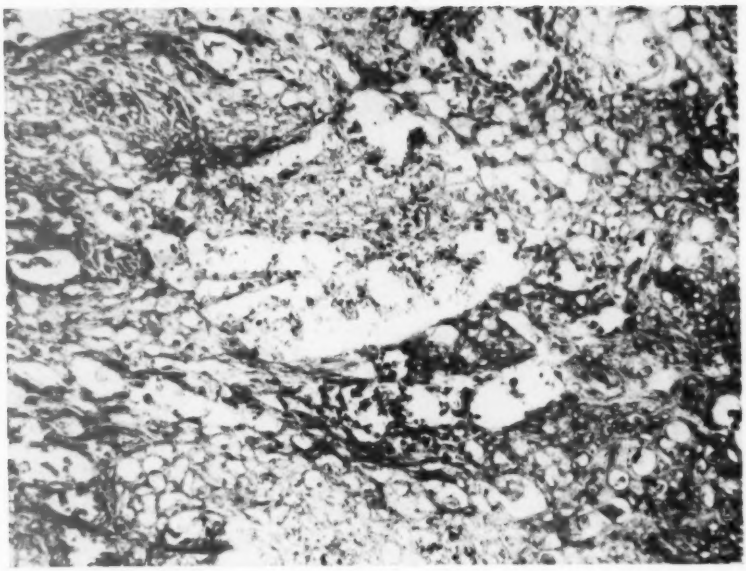

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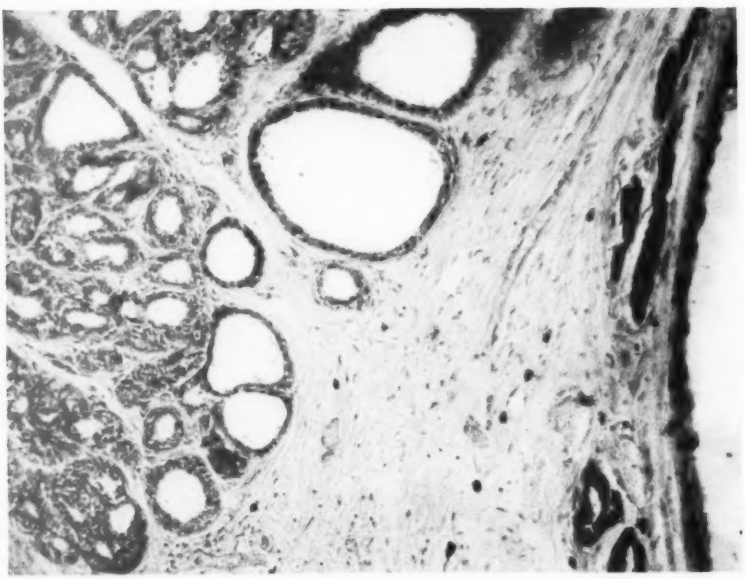

THERAPY OF THE X-IRRADIATION SYNDROME WITH TERRAMYCIN*

M. P. Coulter, M.D., F. W. Furth, M.D., and J. W. Howland, M.D.
(From the Department of Radiation Biology, University of Rochester, School of Medicine and Dentistry, Rochester, N.Y.)

The exposure of an experimental animal to a large dose of whole body x-irradiation results in certain changes in body physiology which become evident as a definite clinical syndrome. The appearance of this radiation syndrome in the dog is very similar to that in man.[1,2] For this reason, the dog is a representative subject for the experimental evaluation of various forms of therapy of acute irradiation injury. Secondary to the direct cytochemical effects of x-irradiation, the major pathologic alterations contributing to the morbidity and mortality following a large dose of whole body x-irradiation may be grouped in five categories: infection, hemorrhagic diathesis, hematologic changes, nutritional and metabolic disturbances. The aspect of the syndrome with which this report is concerned is the nature of the bacterial infection in the x-irradiated dog and the effects of a single antibiotic, terramycin, on the morbidity and mortality.

Previous papers from this laboratory[3,4] have reported a reduction of morbidity and mortality in dogs that received aureomycin after the administration of a large dose of whole body x-irradiation. Those reports presented evidence which indicates the increased susceptibility of the x-irradiated animal to bacterial infections. This is, in part, related to the diminished antigen-antibody response, leukopenia, and destruction of lymphatic tissue which follow exposure to x-irradiation. Terramycin, a non-toxic antibiotic with a wide bacterial spectrum, would appear to be useful in the prophylaxis of a wide variety of infections which may occur during the acute radiation syndrome.

Using oral terramycin alone in two separate experiments, 12 of 13 untreated control dogs given 450 r. of whole body x-irradiation died, while 7 of 14 treated animals exposed to the same dose of irradiation succumbed. The treated dogs showed no delay in morbidity as was previously noted with aureomycin treated dogs.[3] Bacteriologic studies carried out during the course of these experiments showed no apparent difference in the incidence of positive blood cultures between control and treated groups.

Methods

Twenty-seven adult, healthy mongrel dogs were housed in individual

* This paper is based on work performed under contract with the United States Atomic Energy Commission at the University of Rochester Atomic Energy Project, Rochester, N.Y.
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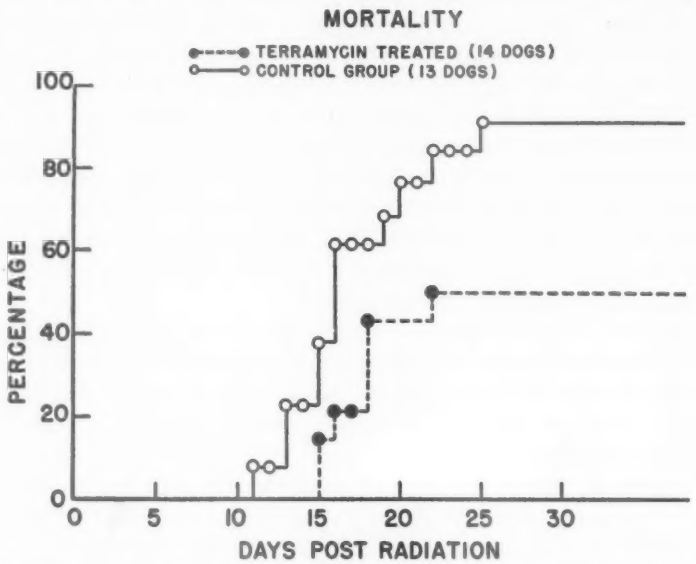
cages and offered water and a soft mash diet *ad libitum*, daily. Thirteen of these dogs served as controls. The remaining 14 dogs received antibiotic therapy post-irradiation. An attempt was made to pair dogs of approximately the same weight and body build in experimental and control groups so that the two groups were comparable. Each dog received 450 r. of whole body x-irradiation under the following conditions: 250 kv., 15 ma., planoconvex aluminum filter with 0.5 mm.



Text-figure 1. Graphic comparison of the total mortality and the time of death following x-irradiation in treated and untreated animals.

copper, target skin distance 40 inches, rate of 7.15 r. per minute. The dogs were radiated in pairs composed of one experimental and one control animal. Immediately following irradiation each of the dogs in the treated group received one 250 mg. capsule of terramycin (approximately 100 mg. per kg. per 24 hours), orally. This medication was continued every 6 hours day and night for 28 days. The animals were weighed twice weekly and examined for evidence of bleeding tendency. A daily record of activity and appetite was kept.

Bacteriologic studies included aerobic and anaerobic blood and necropsy cultures and determination of the *in vitro* sensitivity to both aureomycin and terramycin of the bacteria isolated by a tube dilution method.[4] Hematologic studies, including counts of the erythrocytes, leukocytes, and platelets, were made twice weekly following irradiation. Clinical observations, and hematologic and bacteriologic studies were recorded for a 2-week control period prior to irradiation.

Results

The dogs in both groups showed anorexia and lethargy from the 10th to 20th days post-irradiation. No significant difference in morbidity or bleeding tendencies was noted between the groups. The weight loss was essentially the same in both groups. The red blood cell, white blood cell, and platelet counts showed parallel depressions in both groups of dogs following irradiation.

The first death in the control group occurred on the 11th day post-irradiation, and in the treated group on the 15th day post-irradiation. Text-figure 1 shows that the total 30 day mortality was 92 per cent for the control dogs and 50 per cent for the treated dogs.

Results of the blood culture studies are shown in Table I. There was no significant difference in the percentage of positive blood cultures obtained post-irradiation as compared with pre-irradiation. It is of considerable interest to note that the percentage of positive blood cultures post-irradiation was not higher in the control dogs than in the treated dogs. A blood culture was obtained 24 hours prior to death from 3 of the control dogs. All of these cultures were negative. Blood

Table I
Blood Cultures

	Control dogs		Treated dogs	
	Aerobic	Anaerobic	Aerobic	Anaerobic
Pre-irradiation				
Number of cultures	42	42	42	42
% Positive	10	12	12	17
Post-irradiation				
Number of cultures	95	92	120	118
% Positive	7	12	10	9

cultures were obtained from 5 of the treated dogs 24 hours prior to death. Four of these cultures were positive, 3 showing *Staphylococcus aureus,* and one a strain of Pseudomonas. These same organisms were recovered from necropsy specimens from these animals.

The *in vitro* sensitivity of the bacteria to aureomycin and terramycin is shown in Table II.

Sensitivity of the bacteria from 27 blood and necropsy cultures from control dogs was determined. Thirty per cent of these were resistant (greater than 25 μg. per ml.) to terramycin. Sixty-nine per cent of the bacteria from 16 cultures obtained from treated dogs on which sensitivity determinations were made showed resistance of the same order to terramycin. All of the organisms except for a Proteus

and an unidentified gram-negative rod were relatively sensitive to aureomycin.

Gross pathologic studies revealed no significant differences between

TABLE II

Sensitivity of Bacteria Isolated from Blood and Necropsy Cultures

Dog no.	Source	Organism	Aureomycin	Terramycin
			µg./ml.	µg./ml.
Controls				
1493	Blood	Hem. strep.	1.56	No growth
	Blood	*Staph. albus*	0.195	0.39
	Blood, necropsy	*E. coli*	1.56	3.12
	Spleen, necropsy	Pseudomonas	25.0	6.25
1674	Blood, necropsy	Hem. strep.	0.39	3.12
	Lung, necropsy	*Staph. aureus*	6.25	*100.0
1742	Blood	Hem. strep.	12.5	*100.0
	Lung, necropsy	Non-hem. strep.	12.5	25.0
	Liver, necropsy	*Staph. albus*	1.56	3.12
1730	Blood	Non-hem. strep.	3.12	6.25
	Blood, necropsy	*Staph. aureus*	6.25	*100.0
1736	Blood	Non-hem. strep.	25.0	25.0
	Blood, necropsy	*Staph. aureus*	12.5	*100.0
	Blood	Proteus	100.0	100.0
1682	Blood	*Staph. albus*	12.5	100.0
	Liver, necropsy	*Staph. albus*	0.195	1.56
1680	Blood	*Staph. aureus*	0.195	0.195
	Blood, necropsy	*E. coli*	1.56	6.25
1723	Lung, necropsy	Alkaligenes	0.195	0.195
	Blood, necropsy	*Staph. aureus*	0.195	100.0
1676	Blood	Alkaligenes	0.195	3.12
	Lung, necropsy	*E. coli*	1.56	3.12
	Liver, necropsy	*E. coli*	1.56	1.56
1607	Blood, necropsy	*E. coli*	3.12	1.56
1754	Blood, necropsy	*E. coli*	3.12	12.5
1726	Blood, necropsy	*E. coli*	1.56	3.12
1714	Blood	Gram negative rod	100.0	100.0
Treated				
1738	Blood	Non-hem. strep.	6.25	6.25
1659	Blood	*Staph. albus*	12.5	100.0
	Blood, necropsy	*Staph. aureus*	12.5	*100.0
1746	Blood	*Staph. albus*	12.5	100.0
	Blood	Pseudomonas	25.0	3.12
	Blood, necropsy	Pseudomonas	12.5	6.25
1343	Blood	*Staph. albus*	25.0	*100.0
1720	Blood	*Staph. albus*	0.195	0.195
	Blood	Alkaligenes	0.195	3.12
1741	Blood	*Staph. albus*	25.0	*100.0
	Blood, necropsy	*Staph. aureus*		
1735	Blood	*Staph. albus*	25.0	*100.0
1745	Blood, necropsy	*Staph. aureus*	12.5	*100.0
1743	Blood	*Staph. aureus*	12.5	*100.0
	Blood, necropsy	*Staph. aureus*	6.25	*100.0
1668	Blood, necropsy	*Staph. aureus*	6.25	*100.0
1659	Blood	Gamma strep.	12.5	50.0

* Indicates greater than.

the two groups of dogs. The major derangement contributing to death was hemorrhage. Four animals, 2 treated and 2 control, had severe myocardial hemorrhage. Severe pulmonary hemorrhage and edema occurred in approximately two-thirds of the treated dogs that died and in one-third of the control dogs that died. Ulceration of the mucosa of the small bowel was found in 50 per cent of the dogs that died in each group. None of the dogs in the treated group had blood in the lumen of the large bowel, while one-third of the control dogs that died had large amounts of blood in the bowel. Retroperitoneal hemorrhage extending into the mesentery was observed in 2 dogs in each group. Fifty per cent of the control dogs that died exhibited an extensive area of subcutaneous hemorrhage with ulceration. Similar lesions were noted in 30 per cent of the treated dogs that died.

Discussion

The mechanism whereby an antibiotic is effective in producing alterations in the pathologic physiology of an animal that has received a large dose of x-irradiation is at present obscure. The postulate that most readily presents itself is that these substances are effective in controlling infection and thus exert a favorable influence on morbidity and mortality. There have been many recent reports[5,6] that suggest that infection is an important factor in the x-irradiation syndrome, and the bowel has been implicated as the major source of the bacterial flora which gain access to the blood stream and other tissues following x-irradiation.

A previous paper[3] from this laboratory reported a reduction in morbidity and mortality in dogs that were treated with aureomycin following a large dose of whole body x-irradiation. In that study it was thought that aureomycin was effective in controlling infection. This is attested to by the fact that the incidence of post-irradiation positive blood cultures was higher in the control dogs than in the treated dogs. Also, the bacteria isolated from the control dogs before and after death were sensitive to aureomycin, whereas those isolated from the treated dogs were resistant to aureomycin. If the ulceration which occurs in the small bowel of radiated dogs is related etiologically to intestinal bacteria, the total absence of ulceration in the treated dogs that died in that study indicated further that infection or infectious processes were controlled in those animals.

The observations in this report do not lend similar evidence. At no time was there a higher incidence of positive blood cultures in the con-

trol dogs than in the treated dogs. An increased incidence of positive blood cultures following irradiation was not observed in either group. Pathologic findings at necropsy were similar in both groups and the incidence of ulcers of the small bowel was the same in treated and control animals.

It is of interest to note that there was no reduction in morbidity in the treated dogs as compared with the controls, whereas in the previous study the aureomycin-treated dogs showed both a delay in the onset of morbidity and a reduction in morbidity.

A recent analysis of data collected in this laboratory over a 2-year period indicates that a high incidence of positive blood cultures is not found in the irradiated dog.[7] However, the absence of bacteremia does not necessarily indicate that infection plays no rôle in the irradiation syndrome. It is difficult to evaluate infection in an irradiated animal as the criteria usually used in determining the presence of an infectious process may not be applicable. For example, during the period of post-irradiation when infection is most frequently encountered, the dog exhibits a profound leukopenia. Thus, one of the commonly observed signs, leukocytosis, is absent. In addition, tissue reactions are altered and body defense mechanisms weakened. While the typical response to diffuse pulmonary infection, such as lobar pneumonia, is evidenced microscopically in the normal animal by a massive infiltration of polymorphonuclear leukocytes into the alveoli, in the x-irradiated dog one finds typically hemorrhagic fluid without leukocytic infiltration.[1] This sero-hemorrhagic fluid may not be entirely inflammatory exudate but in part may be edema fluid resulting from transudation through damaged capillaries. Moreover, such increased capillary permeability may occur as a direct result of irradiation, or bacterial exotoxins may play a rôle in the loss of capillary integrity. Amounts of x-irradiation just sub-lethal to the host when administered to the entire body decrease immunity to specific infections and depress antibody formation.[8] The mechanisms whereby immunity is decreased have not yet been fully elucidated. Many think that it can be explained by the marked radiation sensitivity of lymphocytes.[8] These factors illustrate that an infectious process in an irradiated animal may present an unusual clinical and pathologic syndrome and that the depression of immunologic responses may cause the animal to react in a different way from that usually observed.

From existing experimental data there appears to be no adequate explanation for the reduction in mortality in the x-irradiated dog treated with terramycin. In the light of our present knowledge, however, the effectiveness of terramycin in reducing the mortality in these studies can only be assumed to be attributable to the demonstrated

antibacterial activity of the substance, despite the fact that our limited methods of study do not demonstrate the presence of bacterial infection. It is possible that as further progress is made in elucidating the nature and mechanisms of the action of antibiotic substances, a direct favorable effect on diseased and infected tissues may be found in addition to the antibacterial action of these substances. Such an effect is purely conjectural, however, and it is more likely that the effectiveness of those therapeutic agents in allaying the radiation syndrome does rest upon their antibacterial and antiviral potency.

Summary

Treatment of two groups of dogs with clinical doses of oral terramycin following exposure to a large dose of x-irradiation resulted in a reduction in the mortality from 12 of 13 in untreated controls to 7 of 14 in the treated groups.

Treated animals showed no delay in onset of symptoms as was previously noted in animals treated with aureomycin.

Bacteriologic studies showed no apparent difference in the incidence of positive blood cultures between treated and control animals. Thirty per cent of the organisms recovered from control animals were resistant to terramycin; 69 per cent of the organisms from treated animals were resistant.

No differences were noted in hematologic and pathologic observations in the two groups. Severe hemorrhage was the major cause of death observed at necropsy in both groups of animals.

The probable mode of action of terramycin in this reduction in mortality has not been established fully by this investigation.

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PITUITARY NECROSIS IN ROUTINE NECROPSIES*

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Subtotal necrosis of the anterior pituitary body, as it is observed after childbirth, is ascribed to the anoxemia of circulatory disturbance associated with shock and severe hemorrhage. It is not to be expected that an "all or none" law governs this process; one might rather expect intermediate phases between subtotal necrosis and the normal condition. Since severe, irreversible circulatory disturbance naturally may precede death, such necrosis could occur not only in women who have died after childbirth but also in those who have succumbed under other conditions.

Many of the authors who have examined numerous sections of the pituitary gland in various pursuits either do not mention necrosis, or mention it more or less casually. Kraus,[1] in 1926, stated that pituitary necrosis is "by no means rare." Finding small foci of necrosis accidentally in various necropsies induced me to study this problem.

MATERIAL, METHODS, AND FINDINGS

The pituitary glands from 149 necropsies were removed in the usual fashion. They were sectioned horizontally or sagittally, depending upon their shape. Sections were cut at 6 or 7 μ and stained with hematoxylin and eosin. Routinely, 2 sections were taken from each block. There were 2 blocks when the pituitary gland was cut horizontally, and generally 4 when it was cut sagittally.

Necrosis was found 12 times in the routine sections; in one case it was detected on serial sectioning. Numerous sections were cut from most blocks. In many cases series or step series were examined.

The suspicion that such necrotic areas represent post-mortem change will hardly arise. They are surrounded by well preserved tissue and they are present in necropsies done as early as 4 hours, 2 hours, even 1½ hours after death. Neither can they be explained, even the smallest ones, as an exhaustion phase in the secretory cycle.

In 7 cases, only one necrotic focus was found. Serial sections were

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available in 2 of these cases; in 3 others, 100, 70, and 55 sections, respectively. Of the 2 remaining cases, 18 sections each were examined. Three pituitary glands contained 3 foci each; in 3 other cases the number of necrotic foci was 4, 5, and 6, respectively.

Most of the necrotic foci were situated near one of the connective tissue structures, mainly the capsule, but also near the border of the two lobes and near the hilar connective tissue. Twice necrotic glandular tissue occupied a narrow space between capsule and hilum, thus being near a connective tissue structure on more than one side. Necrosis was found also in the cells of the anterior lobe that had migrated into the posterior lobe. The central portion of the anterior lobe seldom was the seat of necrosis. A thin, sometimes very thin, layer of well preserved epithelial cells generally was interposed between the connective tissue structure and the necrotic area. The total volume of necrotic tissue in no case exceeded 1 cc.; it generally was much less. The largest necrotic focus measured 5 mm. in diameter; 2 others, 3 mm.; one, 2 mm. In 4, the size was 1.5 mm.; in 5 others, about 1 mm. Many of the foci were smaller.

There was much variation in shape; most of the subcapsular foci were flat and curved; those near the region of the pars intermedia were mostly round or ovoid. Some were irregular with finger-like protrusions. It was difficult, in such cases, to know whether small necrotic spots were discrete or formed part of one larger focus. None of the foci, when studied in serial sections, was definitely wedge-shaped or pyramidal. The spherical or ellipsoid shape of some was astonishingly regular.

The necrosis mainly involved the epithelial cells; the blood vessels in many foci were more or less preserved and had conspicuous endothelial nuclei. The cytoplasm generally was more severely damaged than the nuclei, but occasionally the reverse was seen. The three cell types showed no difference in their relation to necrosis. The capillaries within the necrotic foci did not differ much from those of the surrounding tissue. They were in most cases wide and filled with well preserved red blood cells. One large necrotic area was surrounded by a thin layer of tissue with narrow capillaries, while capillaries in the necrotic area and in the more remote surroundings were distended.

Necrosis in the masses of basophilic epithelial cells that have migrated into the posterior lobe results in a slightly different picture because the posterior lobe has no network of sinusoids. One necrotic area (2 mm. in diameter) appeared homogeneous. Some of the posterior lobe tissue proper between the epithelial cells had become necrotic also, and its nuclei did not take the stain. No leukocytes were seen,

and there were few red blood cells. The posterior lobe outside the area invaded by the epithelial cells did not show necrosis. In another case, several very small patches of necrosis were scattered through a large area of invading basophils. These small necrotic spots stained intensely with eosin. Such a picture never results from the normal disintegration of the basophilic epithelial cells in the posterior lobe.

Leukocytes were absent in one-third of the lesions; in some cases they were scattered through the dead tissue in various numbers, and were easily recognized by their well stained nuclei. They were situated more in the necrotic tissue itself than in the lumina of the capillaries. In one sharply outlined, round, subcapsular focus the sinusoids were filled with leukocytes. This focus differed from the others in having a narrow zone of edema surrounding it. The tissue around necrotic foci showed very little cellular reaction; usually none at all. No lymphocytes or plasma cells were found. No attempt was made to determine the age of the necrotic process. There were no scars that could be interpreted as the result of necrosis, nor were there any crescent-shaped, subcapsular, fibrous spots. Large, flat, subcapsular areas, which in distribution and shape resembled the foci of necrosis, were present in one specimen. They seemed to consist essentially of wide, blood-filled vessels without leukocytes, of deeply stained colloid, and of various interspersed, non-characteristic nuclei. The remnants of the cytoplasm of the dead epithelial cells were much less conspicuous than in other foci.

The larger and medium-sized blood vessels of the pituitary gland were best studied in the angle between the lobes, and in the hilar connective tissue. With one exception, no important narrowing and no occlusion were found in the cases with necrosis or in those without. In one pituitary gland a small artery in the posterior lobe was narrowed by thrombosis, but the necrosis was in the anterior lobe. No thrombi were found in the necrotic areas, in their neighborhood, or in other portions of the pituitary body.

Up to the age of 50 years (all males, none under 21), the distribution of positive cases over the decades was fairly even (2 of 12 in the third, 2 of 13 in the fourth, 3 of 11 in the fifth). There were 29 pituitary glands from men between 51 and 55 years with 4 positive cases, against only one positive case in the 38 specimens from the second half of the sixth decade. There were 11 cases with necrosis among 60 patients under 55 years, but only 2 cases with necrosis among 94 pituitary glands from men over 55 years of age.

Necrosis caused by tumor masses or by meningitic exudate around the pituitary gland was not included in this paper. In a group of 16

cases with space-occupying intracranial lesions, necrosis was present 3 times. Six of these patients had undergone craniotomy, and necrosis was found in one. Of the 32 cancer cases, 2 had necrosis; of 9 cirrhosis cases and of 19 cases of encephalomalacia, 1 each. Hypertension had been an outstanding symptom in 11 patients and 4 of them had necrosis, 2 after sympathectomy.

The clinical conditions in the last days of life were not uniform. While in some patients shock and severe peripheral circulatory failure were noted, necrotic areas were present in 2 patients who had died unexpectedly and rapidly.

Microscopic sections and some data of 11 other cases of pituitary necrosis (from Beth Israel Hospital, New York City) were available. They could not be evaluated statistically because the data on the corresponding negative cases were lacking. But it may be useful to enumerate the diseases and conditions mentioned in all 24 cases in which pituitary necrosis was found: diabetes, 2; chronic renal disease, 3; essential hypertension, 2; intracranial hemorrhage, 2; encephalomalacia, 3; severe acute hemorrhage, 4; major operation in the last 2 weeks of life, 6 (3 of these craniotomy); shock in the last 2 weeks of life, 4.

Comment

Comment on clinical correlations can be short. The material, in most respects, is too small for detailed statistical evaluation. The older age groups and those with encephalomalacia yielded far fewer cases of pituitary necrosis than hypertensive patients and those of younger age groups. This may indicate that anatomical narrowing of arteries is less conducive to pituitary necrosis than vascular dysfunction, notably hyper-reactivity. It remains to be seen whether the occurrence in 2 patients following sympathectomy is accidental or meaningful. One died 8 hours after operation. According to Sheehan and Murdoch,[2] pituitary necrosis takes at least 14 hours to develop.

Scars in the pituitary gland are rare because the necrosis generally occurs under conditions that lead to death. Sheehan and Murdoch,[2] however, have found small scars in women who, years before, had gone through severe obstetric illness. Probably, the pituitary gland during pregnancy is so susceptible that necrosis can take place in it even under non-fatal conditions.

The rôle of embolization in the genesis of pituitary necrosis will be discussed on the assumption that subtotal necrosis after delivery and small foci of asymptomatic necrosis represent different degrees of the same process. Before Sheehan's[3] work, it was almost generally assumed that pituitary necrosis was caused by embolic occlusion of blood

vessels. The terms necrosis, ischemic necrosis, embolic necrosis, and infarct are used interchangeably in the older literature. In his classical paper on fatal destruction of the pituitary gland, Simmonds[4] took it for granted that the lesion in the pituitary gland was embolic. He stated, however, that the larger vessels were normal. In several papers, Simmonds[5-8] referred to septic diseases in which he found emboli of bacteria and foci of necrosis in the pituitary body. He designated the lesion in one of his cases as embolic necrosis. He stressed the absence of changes in the walls of blood vessels.

Simmonds[8] was aware of the multiple blood supply of the pituitary gland as found by Luschka[9] and by Dandy and Goetsch.[10] With Luschka he believed that the numerous small vessels that run to the anterior lobe from the stalk were arteries. He realized that the occurrence of infarcts is inconsistent with multiple blood supply. He therefore asked Benda to reinvestigate the blood supply of the pituitary gland. Benda[11] came to the conclusion that the small vessels running along the stalk enter only the posterior lobe, and that the anterior lobe receives its blood mainly through one small artery coming from the carotid within the cavernous sinus. In this Simmonds found confirmation of his opinion that the pituitary lesions described by him were embolic. He wrote that this new statement pleased him very much because now larger embolic lesions of the anterior lobe became understandable.

A glance at the photographs of lesions described by Simmonds as embolic indicates that many of them are identical with the ones described in this paper. The septic nature of Simmonds' cases may have been a factor in the causation of necrosis, but I do not believe that the lesions were embolic. One of Simmonds' papers[7] on embolic processes in the hypophysis included a case of complete necrosis of the anterior half of the anterior lobe. This patient had died of heart disease 7 days after delivery, and there was no sepsis. The lesion was called anemic infarct occasioned by childbirth. None of the illustrations in Simmonds' papers shows a plug in a pituitary vessel of adequate size.

Among the pituitary lesions which I[12] described in 1922, only 2 were examples of necrosis in the anterior lobe (cases 9 and 16). I called them infarcts, erroneously, as I think today. Baló[13] mentioned arteries obliterated by emboli in one case of pituitary necrosis, and postulated them in another one. Both were young diabetic patients with pulmonary tuberculosis. Kraus,[1] in a pituitary gland with necrosis, found an artery occluded by intimal overgrowth. The patient was a woman, 61 years of age, with diabetes and hypertension. Kraus

stated that necrosis in young diabetic patients with an intact vascular system is entirely unexplained. He stressed the discrepancy between the two facts that the anterior lobe is so rich in blood vessels, and that necrosis is found mainly in circulatory disorders.*

Kaminsky,[14] to my knowledge, was the first to deny the embolic origin of pituitary necrosis. He mentioned the possible importance of difficult deliveries and uterine hemorrhage. Sheehan, in his paper of 1937,[3] explained post-partum necrosis by thrombosis of the sinusoids in the anterior lobe. He found some sinusoids thrombosed, but never a larger vessel, and he did not see widespread capillary thrombosis. He realized the difficulty of proving the causative rôle of the thrombi. In a later paper,[2] he gave an explanation—which he considered quite speculative—namely, that the blood flow to the involuting anterior lobe is physiologically reduced at the time of delivery and that shock reduces it further, bringing on thrombosis. The extent of thrombosis as described by Sheehan makes it appear more as a concomitant of the necrosis than as its cause. It also is difficult to think that capillary thrombosis sufficient to bring on almost complete necrosis should be restricted to the anterior pituitary lobe. Such selectivity is more easily understood as corresponding to metabolic than to circulatory properties.

With the confirmation that Luschka's concept of the blood supply of the pituitary gland has received by modern anatomists,[15] the doubts are revived which Simmonds originally entertained concerning the possibility of infarction in the pituitary gland. The modifications of Luschka's concept which resulted from the work of Wislocki[15] do not alter the situation; the fact remains that blood reaches the anterior lobe by many channels. In addition to arteries which enter the groove between the lobes, a number of vessels run alongside the stalk and enter the anterior lobe. They are veins, but the blood in them flows toward the pituitary gland; they are called the hypophyseo-portal vessels.

The early work on pituitary necrosis was largely done on septic diseases. This fact in itself made an embolic origin plausible. Today I do not understand why the blandness of the lesions in the anterior lobe, as opposed to the abscess-like metastases in the posterior lobe, did not deter pathologists from the embolization theory. The thin layer of well preserved tissue which often lies between the area of necrosis and the capsule enhances the similarity to infarction, but several considerations speak against infarction, in addition to the fact that occlusion

* No attempt is made to enumerate all papers on pituitary necrosis. For a detailed discussion of the older literature see Sheehan.[3]

of a hypophyseal artery has seldom been found. The necrotic areas are not hemorrhagic, and it is improbable that infarction in an organ with so many wide, thin-walled sinusoids should not lead to diapedesis of red blood cells. The regularly ellipsoid, sometimes spherical shape speaks against infarction. In most cases of pituitary necrosis there are no embolic phenomena in other organs, especially not in the brain. We would have to assume that embolization restricted to one small organ occurs frequently in a variety of cases and in the absence of a manifest source of the emboli. Such predilection of emboli for the anterior pituitary gland would, *a fortiori,* make us expect them in pituitary vessels when other branches of the internal carotid do contain emboli. But I searched, without success, 50 sections of the pituitary gland in a case of septic (endocarditic) embolization of both middle cerebral arteries. If occlusion of arteries was the main factor, one should expect an increase with age and with cerebral vascular disease. This, to judge from the material at hand, is not the case.

Two instances may further illustrate the fact that pituitary necrosis and mechanical occlusion of pituitary vessels do not go hand in hand: When a patient dies in malarial coma and pituitary necrosis is found, one would expect the pituitary sinusoids to be blocked by parasites, but Guccione[16] stated that there were no parasites in the sinusoids. He thought of a toxic factor causing the necrosis. In a patient who had died of clinically latent gastric carcinoma with generalized arterial metastases, I found numerous capillaries filled with carcinoma in the anterior lobe. There was no tissue reaction around the tumor emboli, but a small area of necrosis was found in a portion of the anterior lobe that was free of emboli. In each case, the seemingly obvious connection between necrosis and occlusion of capillaries did not exist.

Pituitary lesions might be expected in so-called temporal arteritis which affects the carotid system especially. In a paper on temporal arteritis[17] a report on a necropsy contains the statement, "pituitary gland appears necrotic" (no details given). Dr. Jennings,[18] at my request, had new sections made of the pituitary gland. He found "very small foci of necrosis" and "no marked vascular change." He thinks, however, that the pathologist who first studied this gland did find changes in the vessels and ascribed the necrosis to them. These small foci of necrosis probably were accidental, but one should pay attention to the pituitary vessels in cranial arteritis; the neighboring ophthalmic vessels are often affected.

It would be unwise to deny that vascular occlusion can lead to necrosis in the pituitary gland. When, for instance, in an 81-year-old man one large hypophyseal artery was almost occluded by the thick-

ened intima, it might be assumed that this could have been one factor in the genesis of the necrotic areas in the anterior lobe; but, since necrosis occurs when all vessels are normal, we cannot attach much importance to the narrowing or occlusion of single arteries. Necrosis could not be detected in the pituitary gland of a young man who died 1 week after ligation of the right internal carotid artery. Necrosis does not occur in the posterior lobe under ordinary conditions. The basophilic epithelial cells, which normally invade the posterior lobe, do not bring blood vessels with them, but migrate individually. Thus, being in an organ in which necrosis does not occur, these cells should be immune from necrosis. The fact that they do become necrotic clearly shows that the cause of necrosis lies in the cells themselves and not in embolic or thrombotic occlusion of blood vessels.

It was to be expected that pituitary necrosis, when found in unusual or unexplained diseases, would be considered an essential part of the picture. But, in my opinion, the necrotic lesions reported in beriberi,[19] as well as in renal rickets,[20] were accidental findings.

The idea presents itself that pituitary necrosis might be related to altered endocrine function. It is supported by the severity and relative frequency in the puerperal state when the organ has gone through the changes of pregnancy. Endocrinologic diseases, however, as far as I know, do not supply many instances of pituitary necrosis. Diabetes is an exception. The number of examples in diabetic patients in the older reports is astonishing, and some of these necrotic lesions were unusually large. At least 4 cases are on record in which the urine of a diabetic patient became free of sugar some time before death, insulin was discontinued, the blood sugar was normal, and at necropsy the anterior pituitary gland was found widely necrotic.[21-23]

The question arises whether such necrosis occurring in the last days of life, independently from occlusion of vessels, is a prerogative of the master gland. The one other organ that shows similar necrosis is the adrenal cortex, which is functionally related to the pituitary gland and which has several anatomical features in common with it: the relation between cells and sinusoids, the combination with a nerve structure, and the multiple blood supply. In my material, such necrosis was found only once in the adrenal gland. The main finding in that 63-year-old man was aneurysm of the left ventricle with massive pulmonary infarction. Necrosis was not found in the carefully examined pituitary gland. The adrenal gland was searched for vascular lesions, but none was found. Focal necrosis of the adrenal cortex was found 18 times in the single routine sections of 3,080 necropsies (Mitchell and Angrist[24]). Nine of these may be comparable to pituitary necro-

sis. Mitchell and Angrist do not state if they ever found necrosis in the pituitary and adrenal glands in the same necropsy. An infectious disease process was present in most of their cases.

The hemorrhagic necrosis which Crawford[25] found in the suprarenal glands of 14 pregnant women belongs to another chapter.

The condition of the blood vessels presents an important difference between renal cortical necrosis and pituitary necrosis, which have been found together repeatedly. In the latter, no anatomical vascular lesions exist; in the former, most cases show fibrinoid change in the vessels, necrosis, or true arteritis. Obviously the sets of conditions that are responsible for each lesion have several items in common, pregnancy being the most important. The extent of the pituitary necrosis found in cases of renal cortical necrosis varies from subtotal (Doniach[26]) to small areas similar to those with which this paper is dealing (MacGillivray,[27] case 3).

The foregoing observations and considerations that speak against an embolic or thrombotic origin for pituitary necrosis are given additional weight by the occurrence of necrosis in the masses of epithelium which extend into the posterior lobe. The posterior lobe tissue itself does not participate to any marked degree in the necrosis, even in very severe cases. Since we thus cannot incriminate the vasculature of the posterior lobe, we must find the main cause for the necrosis in the cells themselves. Probably the pituitary epithelial cells are in a precariously labile equilibrium, sensitive to deficiency of oxygen or to accumulating products of metabolism. As Victor and Andersen[28] pointed out, the metabolic rate of the rat's pituitary gland at the time of parturition is about three times as high as in any other phase of reproduction in the rat. If it is the same with the human pituitary gland, we have an explanation for the massiveness of the post-partum necrosis.[29] In the less susceptible pituitary glands of non-pregnant women and of men, shock-like conditions which precede death cause only small foci of necrosis. I do not know if the oxygen consumption of the anterior pituitary gland is higher than that of other organs, especially endocrine organs. The anterior lobe cells are at a disadvantage as far as metabolism is concerned because they receive much venous blood through the hypophyseo-portal vessels. It is a matter of speculation how far vasospasm, as part of the shock syndrome, is a causative factor (Giornelli,[30] Plaut[31]).

Finally, among the probably multiple causative factors, a mechanical one may be active. The small necrotic foci are mostly near one of the non-yielding connective tissue structures, and the pituitary gland at the end of pregnancy is tightly squeezed into the sella. In one case

of subtotal post-partum necrosis (Gotshalk and Tilden[22]), a portion of the anterior lobe protruded from the sella and did not participate in the necrosis. In another condition, however, which leads to hyperplastic enlargement of the pituitary gland, namely, increased intracranial pressure, necrosis of the anterior lobe is not conspicuous.

Summary

In 149 unselected necropsies of adult males, necrosis in the anterior pituitary gland was found 13 times.

In none could necrosis be explained by embolic or thrombotic occlusion of blood vessels. It appears that most of the necrotic lesions in the anterior lobe which might have been described as embolic or thrombotic are not of such origin.

Necrosis was less frequent after the age of 55; it seemed to be frequent in hypertension. Otherwise, no correlation with clinical disease was evident.

The subtotal post-partum necrosis of the anterior pituitary gland (Sheehan[2]) represents an exaggerated degree of a process that takes place frequently during the last days of life, in non-pregnant women and in males, without a close relationship to the disease from which the patient is dying.

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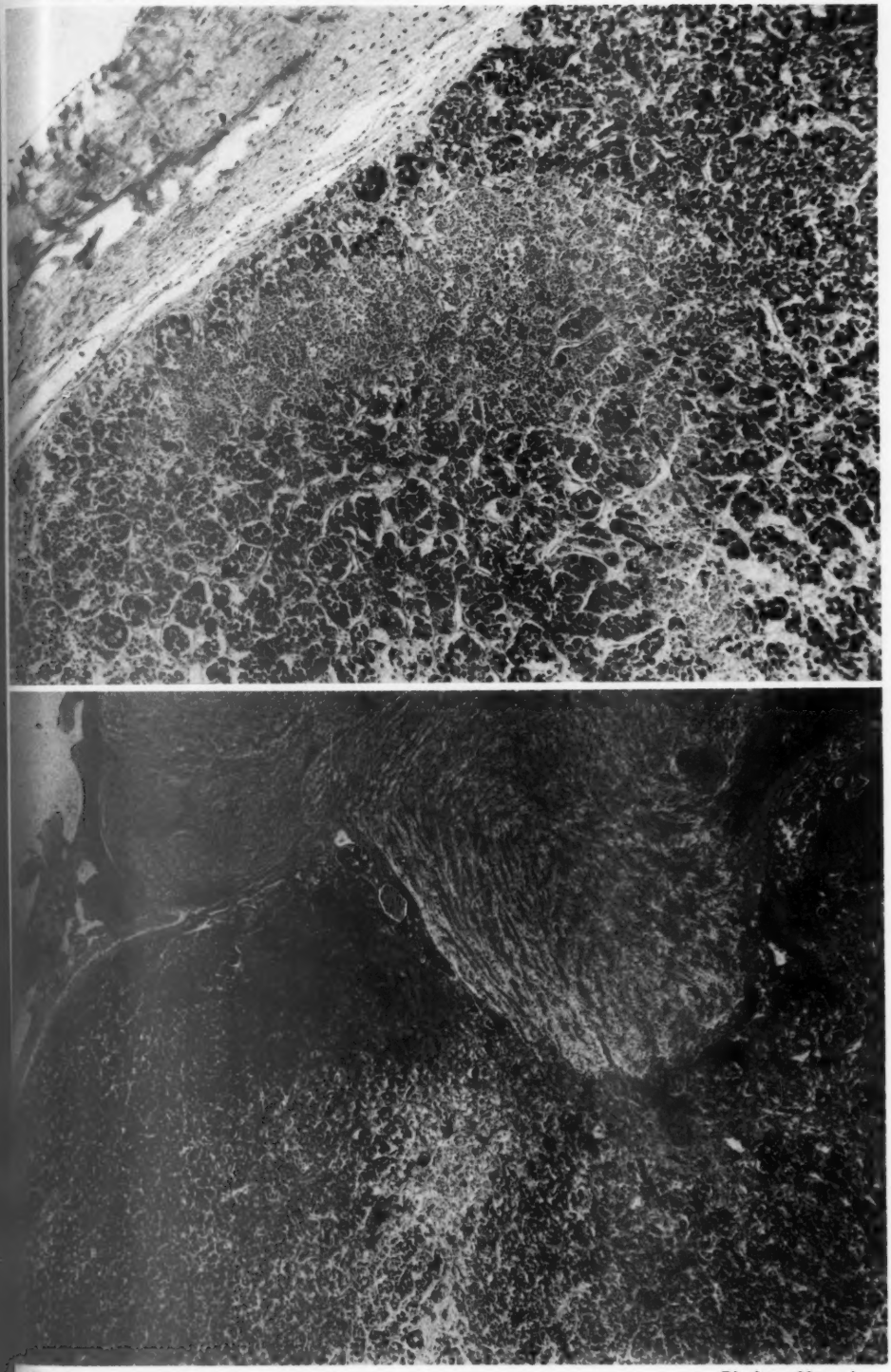
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 136

FIG. 1. Typical subcapsular necrosis. A thin, somewhat interrupted layer of well preserved tissue lies between the region of necrosis and the capsule. In the right lower corner, necrosis extends deeper into the tissue. Male, 51 years old, with abdominal carcinomatosis. Hematoxylin and eosin stain. × 77.

FIG. 2. Irregularly rounded area of necrosis in anterior lobe near the base of the stalk. The necrotic tissue is deeply stained with eosin and, therefore, appears dark. The clear area near the necrotic focus is normal connective tissue. Male, 46 years of age, with essential hypertension; sympathectomy. Hematoxylin and eosin stain. × 18.

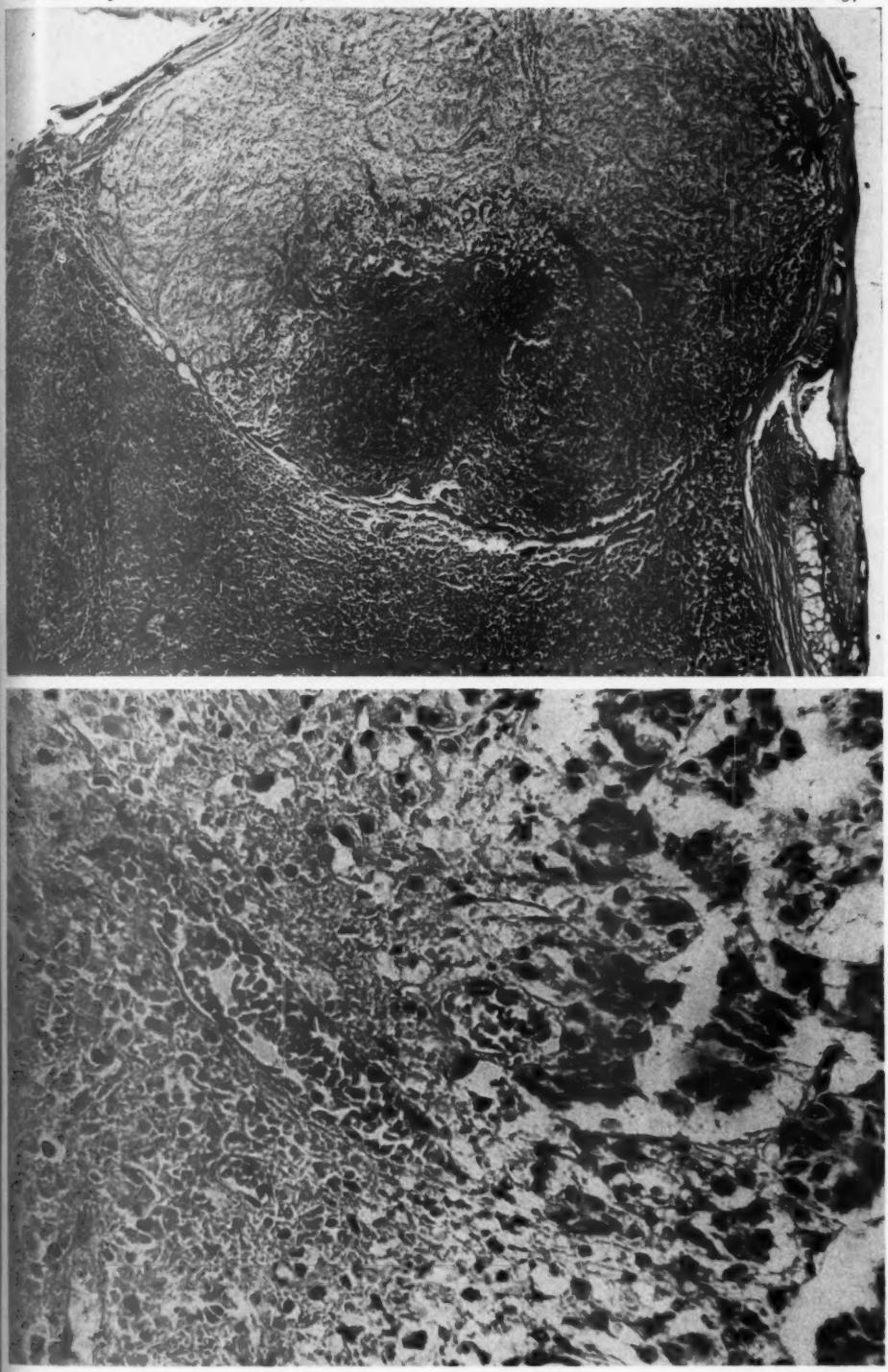


Plaut Pituitary Necrosis

PLATE 137

FIG. 3. The posterior lobe (above) is widely invaded by epithelial cells; a large portion of this epithelium is necrotic (center of field). The surrounding posterior lobe tissue is normal. Female, 70 years old, with carcinoma of the bladder. Hematoxylin and eosin stain. × 18.

FIG. 4. Edge of necrotic focus. Single nuclei are preserved. A capillary in the necrotic area is distended with red cells. There is no inflammatory reaction. Female, 36 years of age, with peritonitis. Hematoxylin and eosin stain. × 385.

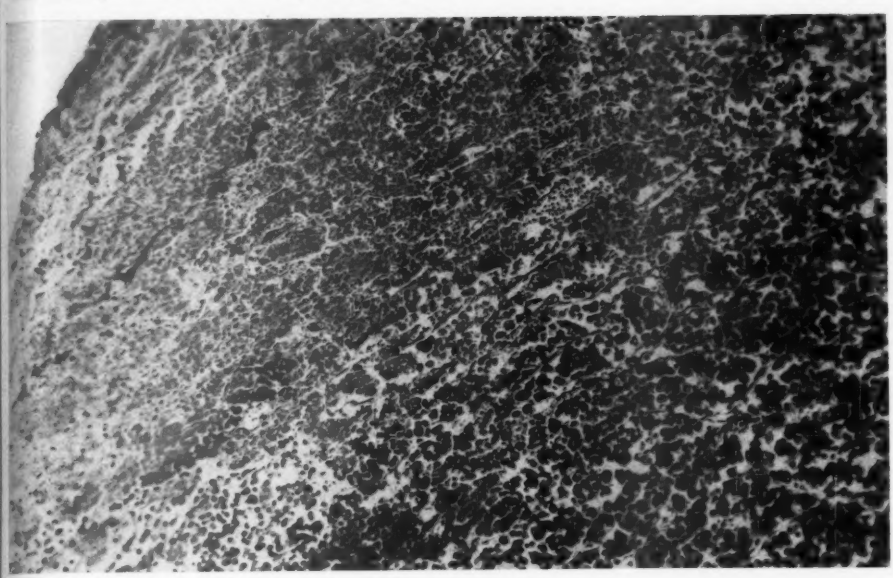


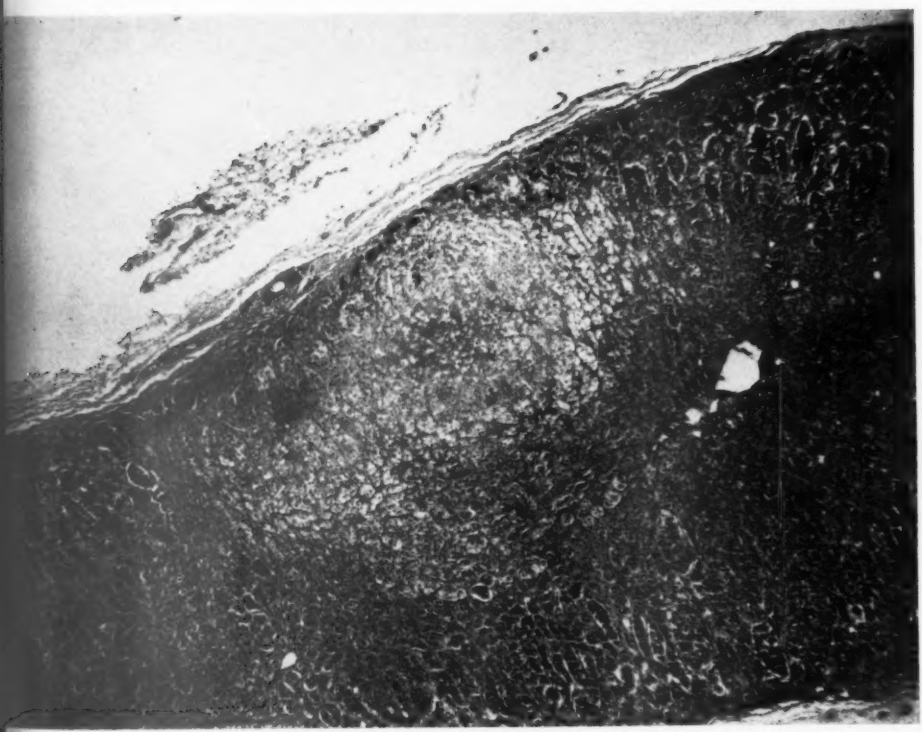
Plaut Pituitary Necrosis

PLATE 138

FIG. 5. Necrosis in anterior lobe, similar to that shown in Figure 1. Necropsy 1,435/1919 (Eppendorf Hospital, Hamburg); male, 18 years old, with otogenous septic thrombosis of transverse sinus. Inflammation is absent. This focus was erroneously considered as embolic. Iron hematoxylin stain. × 110.

FIG. 6. Subcapsular necrosis in adrenal cortex. There is a similarity to pituitary necrosis. Male, 63 years old, with aneurysm of left ventricle and massive pulmonary infarction. No necrotic foci were found in the pituitary gland. Iron hematoxylin stain. × 40.





Plaut Pituitary Necrosis

EXPERIMENTAL COCCIDIOIDAL GRANULOMA

Developmental Stages of Sporangia in Mice *

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The purpose of the present investigation has been to observe the steps by which cultured filaments of *Coccidioides immitis* develop into parasitic spherules when injected into mice, and to note the histopathologic responses of the host which accompany the detailed changes in the fungus.

For those not familiar with this microorganism, it may be said that *C. immitis* is a filamentous fungus which grows readily as a colonial mat on the usual culture media employed in mycologic study. As the colony ages, some of the hyphae differentiate into arthrospores (Fig. 1). When introduced into the tissues of certain laboratory animals, the cells of the microorganism assume a different form, that of a spherule (Fig. 14), which is the only form normally seen in infected animal tissues. The spherule undergoes a definite cycle of growth and reproduction.

The earliest descriptions of the spherules of *C. immitis*, as they appeared in necropsy material from the first known cases of coccidioidomycosis, were those of Posada[1] and Wernicke.[2] The saphrophytic phase of the fungus was discovered 8 years later (1900) by Ophüls and Moffitt.[3] Many subsequent investigators have published observations on the developmental cycle of *C. immitis*.[4-13] A culminating study is that of Baker, Mrak, and Smith.[14] They reviewed the literature on morphology.

A number of workers have contributed to the elucidation of the process by which the cultured filaments of *C. immitis* change into spherules upon injection into animals. In 1904, Wolbach[15] reported seeing chains of hyphae with increased size and rounded form in lesions in the rabbit 48 hours after injection of material from cultures. Ophüls[16] noted that the spherical forms developed by direct enlargement from the rectangular cells of the fungus in the tissues of the guinea-pig. It was his opinion that only the arthrospores underwent

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transformation. Using an inoculum from very young cultures before arthrospores had appeared, Chope[17] demonstrated that undifferentiated cells as well as arthrospores develop into spherules in guinea-pigs. He reported that most of the injected hyphae were still intact on the third day, but that some rounded cells connected together were present as early as the second day. Moore[18] reported that undifferentiated cultural elements were first converted into arthrospores and then into spherules when planted on the chorioallantoic membrane of the embryonated chicken egg. Tager and Liebow[19] could not trace the early stages of development of the spherules with certainty in intranasally infected mice sacrificed between 9 hours and 4 days after inoculation.

With the exceptions just mentioned, most studies of the spherules of *C. immitis* have been based upon its appearance in mature granulomatous lesions. To a great extent this also applies to studies of the tissue responses of the host in coccidioidomycosis. The mixed type of granulomatous inflammation which characterizes the late stages of the disease is well known from studies of post-mortem material obtained from human cases. But there is as yet little direct knowledge concerning the early morphologic aspects of the infection. Tager and Liebow[19] pointed out that earlier investigators, such as Ophüls[8,16] and Rixford and Gilchrist,[13] had emphasized the polymorphonuclear phase of the infection; and they stated that Ophüls attempted to correlate the nature of the reaction with the type of spherule present. Working with experimental coccidioidal infection in mice, Tager and Liebow noted that classical tubercles were conspicuous by their absence and they believed that the chief acute reaction was polymorphonuclear in type, at first without necrosis but soon associated with abscess formation and death of the tissues. In general, however, they were in agreement with the observations of Ophüls in that the endosporulating spherules are more commonly associated with the abscess of the acute lesion, while the adult forms are more characteristic of chronic infection. Forbus[20] clarified the histologic pattern, emphasizing that the spherule is a microorganism with a complex life cycle, each stage of which must influence the action of inflammatory cells in a different way. He derived the early host responses from analysis of mature lesions in human coccidioidomycosis and pointed out that the initial tissue response to the invading microorganism might be purely polymorphonuclear.

More experimental studies of early coccidioidal infection, employing animal inoculation, appear to be required for a fuller understanding of the initial changes in both fungus and host.

Methods and Materials

Source of Inoculum. Pus containing spherules of *C. immitis* was obtained by aspiration of subcutaneous abscesses from a patient with known coccidioidomycosis. An injection of 0.1 cc. of the pus was made intraperitoneally in each of 12 ABC mice. The first death among the inoculated mice occurred in 11 days. The surviving mice were then destroyed by etherization. The dead mice were submerged for 15 minutes in 70 per cent ethyl alcohol containing 2.5 per cent tincture of iodine. The mice were fastened to a board, the base of which was covered with gauze soaked in phenolor. Their abdomens were opened aseptically and the granulomatous greater omentum grasped with small forceps and removed with iris scissors. The omenta of the mice were pooled in 25 cc. of physiologic saline solution containing 50 units each of penicillin and streptomycin per cc., and broken to a fine-particle size in a Ten Brock tissue grinder.

Inoculum. Fifty cc. quantities of mycophil broth were placed in 125 cc. cotton-stoppered Erlenmeyer flasks and sterilized. One-half cc. of the preparation of mouse omentum was then added to each flask. The cultures were overlaid with 20 cc. of sterile mineral oil and incubated at room temperature.

Numerous small, undifferentiated, filamentous colonies of *C. immitis* developed in the broth below the oil in 4 to 5 days. The excess broth was then aspirated and discarded. The remainder of the broth, containing a concentrated suspension of fungi, was drawn into a wide-mouthed pipet with care to exclude the mineral oil and transferred for homogenization to a Ten Brock tissue grinder. As many microorganisms as possible were used in the inoculum in an effort to facilitate the location of the fungus cells in the body of the mouse during the first 24 hours of infection. The inoculum was milky to the eye. An average of 11 mycelial fragments per field was counted in wet mounts, employing a magnification of $\times$ 430.

Procedure. Each of 50 male ABC mice of roughly 25 gm. and of approximately like age was given 0.5 cc. of the inoculum intraperitoneally. Four mice were killed by etherization and examined at 4, 6, 20, 24, 30, and 48 hours after inoculation. Thereafter 2 mice were killed daily until the 14th day. Four mice were allowed to progress to the terminal stages of the infection. These mice died between the 21st and the 24th day after inoculation. The abdomens of all mice were opened and examined for any gross evidence of infection. Smears were prepared from peritoneal fluid and small sections of tissue. These were stained by the Giemsa method. Portions of omentum, liver,

spleen, and other organs were fixed for histologic study. Alternate paraffin sections of the specimens were stained with hematoxylin and eosin, and by the Hotchkiss-McManus technic.[21] Serial sections were made from some blocks for the study of the three-dimensional structure of spherules.

Observations

At 4 and 6 hours after inoculation no gross abnormalities could be seen. The material injected was diluted with a serous exudate and dispersed in the peritoneal cavity. The fragments of mycelium were difficult to find and showed no change in form. At 20 hours no macroscopic lesions were observed, but smears from the peritoneal surfaces revealed a few microscopic masses of approximately spherical shape measuring about 100 μ in diameter. The masses consisted of aggregations of hyphal elements infiltrated with and surrounded by polymorphonuclear leukocytes (Figs. 2, 3, and 5). A few of the fungus cells in the masses were observed to have become spherical or ovoid (Fig. 4). These organisms were basophilic in their staining properties. They possessed a double-contoured wall about 1 μ thick, a polar or peripheral concentration of the protoplasm, and varied from 3 to 8 μ in diameter. Such cells were not numerous.

A few masses similar to those described had become visible to the eye as yellowish white dots on the peritoneal surfaces at 24 and 30 hours. Microscopically, this increase in size was due to the greater number of polymorphonuclear cells surrounding the aggregated mycelium. The masses were most frequently seen in the vicinity of the spleen, liver, and stomach, but they also occurred elsewhere. In some of the masses the mycelium showed branching (Fig. 2).

The first indication that some of the masses of polymorphonuclear cells and mycelium were becoming fixed to the tissue appeared at 30 and 48 hours. Such a mass would adhere to the point of a dissecting needle and could easily be picked up, but some resistance was noticed. A mucoid thread connecting the mass with the surface of the tissue was drawn out with it for a short distance. Microscopic examination of paraffin sections through such masses (Fig. 6) disclosed their structure to be essentially the same as that of the ones previously described, except that now each mass appeared to be covered with mucoid material containing a few mononuclear cells. The mucoid material possessed an alveolar structure and retained hematoxylin. In some instances it appeared to be continuous over the mass and that portion of the tissue surface immediately adjacent to it. In those tissues where attachment had occurred there was a moderate local mononuclear and polymorphonuclear inflammatory response. A few spherical fungus cells were

occasionally found in this tissue (Fig. 7). A change in the distribution of the fungus elements had occurred in many of the masses at 30 and 48 hours. The fungus cells were now located peripherally where earlier they had occupied a central position (Figs. 6 and 7). In those masses having a peripheral arrangement of the fungus elements, the core of the mass was in many instances composed of amorphous, poorly staining material.

The masses were found more deeply imbedded in the omentum through the third and subsequent days (Figs. 7 and 8) and more of the fungus cells possessed a spherical form. But masses containing mycelium were still found in the tissues for as long as 96 hours. Only a portion of the injected mycelium underwent the change to spherules. The greater part of it remained in the center or periphery of masses and by the fourth day the outline of this mycelium was poorly defined and its ability to take stains was impaired. No recognizable mycelium was seen after 4 days.

The number of young spherules microscopically visible in the tissues increased from the third day after inoculation. But there was no evidence of multiplication of the spherules until a much later time. Although they increased in size, the first generation of young spherules remained uniform in appearance until about the fifth day (Fig. 9). The tissue response remained predominantly polymorphonuclear, but as early as the fourth day a few of the larger spherules were found to be the center of mononuclear activity (Fig. 10). Later (6 to 7 days) many of the larger maturing spherules of the first generation were surrounded by mononuclear elements (Figs. 11 and 12).

During the fifth, sixth, and seventh days, a number of the spherules had reached the early stages of cleavage (Fig. 10). Their average diameter was 40 μ, with a variation of 15 to 65 μ. In all of them the protoplasm was distributed peripherally around a central vacuole. The small, deeply staining bodies in the protoplasm were more numerous. The first actual evidence of cleavage was the appearance of radial partitions between the deeply staining bodies. Subsequent cleavage planes appeared to be laid down at angles to those preceding. During the stages of cleavage the immature endospores became more numerous and of diminishing size. They were sharply angular (Fig. 12). When mature, however, the endospores were round.

On the sixth and seventh days, fully developed sporangia could be found with diameters as great as 93 μ. The double-contoured walls of these sporangia were intact. Intact sporangia and other large spherules usually were surrounded by epithelioid cells. Sporangia whose walls had ruptured were first discovered on the seventh day. Later they

were much more numerous (Fig. 13). The ripe sporangia contained hundreds of spherical endospores measuring from 1 to 3 μ in diameter. A study of serial sections of sporangia showed that the great majority of those which ruptured possessed relatively thin walls (1 to 3 μ thick), and that the walls of many of them had broken open at more than one place. Polymorphonuclear cells were always present in the vicinity of sporangia which had ruptured.

From the 7th to the 14th day, an increasing number of new lesions, both gross and microscopic, made their appearance in the peritoneal cavity. Lesions appeared in other membranes than the omentum and sometimes upon the surfaces of organs not hitherto involved, and in the parietal peritoneal wall. The fungus population of the tissues became increasingly varied as to developmental stage. There were huge numbers of endospores. By 10 days, spherules of various sizes and forms were seen in every microscopic field (Fig. 14). The life cycle of the parasite, which had unfolded in a fairly orderly fashion during the first few days, with all of the fungi at about the same developmental stage, had now become completely out of phase. The inflammatory response was also of a mixed nature. The pathologic expressions of the disease varied from focus to focus in the same lesion. In some foci the reaction was leukocytic, while in neighboring foci it was epithelioid. Foci in transitional stages of inflammation between the two were present. The smaller spherules (roughly up to 30 μ in diameter) were associated with the polymorphonuclear inflammation, while the larger forms tended to be the center of predominantly reticulo-endothelial activity.

Certain aberrant spherules were encountered. Among these were spherules which possessed walls much thicker than the average (4 to 8 μ), some of which were distorted and eosinophilic (Figs. 15 and 18); spherules of enormous size (to 90 μ in diameter) without cleavage planes or other indication of reproductive activity (Fig. 16); sporangia in which cleavage had evidently ceased in an early stage, resulting in the formation of giant endospores (Fig. 17).

Discussion

The purpose of this work was to study the early changes in *C. immitis* and the corresponding host response when mycelium was placed in the peritoneal cavity of the mouse. We were alert to the fact that this two-fold process is a dynamic one and realized the inherent limitations in our observations, which were, in a sense, a series of microscopic "stills." But we are confident that sufficient sampling has been accomplished so that the pattern of interaction can be constructed.

During the first few hours after injection of *C. immitis* into the peritoneal cavity, the fungus elements were difficult to find, indicating that dispersion and dilution had occurred. This was the only indication of host response. No evidence of growth or morphologic change in the fungus was seen. Probably this interval represents an adaptation period for both parasite and host. By 20 hours, however, agglutination of the mycelial fragments had occurred and the aggregates were surrounded and infiltrated by polymorphonuclear cells. This agglutination of the mycelial fragments occurred too promptly to be the result of a specific antigen-antibody reaction, and most likely resulted from the action of non-specific agglutinating substances innate to the peritoneal fluid or from mechanical movements of the peritoneal fluid or abdominal structures.

Early spherule formation was first observed among the aggregated mycelial filaments in 24 hours. The newly formed spherules developed by rounding and direct enlargement of mycelial cells. This is in keeping with the observations reported by other investigators.[14-18] The majority of the mycelial cells, however, never underwent the change and eventually disintegrated. These cells may have been injured or killed during the preparation of the inoculum. It is also possible that they lacked environmental adaptability owing to immaturity or to individual cell characteristics. The possibility should also be considered that the mouse may have some innate ability to destroy this organism. Considerable branching of the aggregrated mycelium was noted, suggesting that the filaments of *C. immitis* may have continued to grow for a short time. We could not be certain of this as many of the injected hyphae possessed branches.

As long as the aggregates of mycelium remained free in the peritoneal cavity, the primary host response was polymorphonuclear. The leukocytes continued to be attracted until, by the second day, their huge number visibly marked the site of such aggregates. At this time some of these pin-point lesions were found to be loosely attached to the surface of the peritoneum. Microscopic examination revealed that these masses were now imbedded in, and surrounded by, a mucoid material. This material played an important rôle in the course of the infection since it acted as an adhesive in fixing the masses to the peritoneum. At first acellular, the mucoid material later contained a few mononuclear cells. We were not able to determine the origin of this substance. By the third day the masses were firmly attached to the peritoneal surface and a cellular response was present in areas of the tissue adjacent to them. A few small spherules could be identified in this tissue. The exact means by which the fungus gained entrance into

the tissues is not certain; however, it is our opinion that invasion occurs as follows. At the site of attachment of the mass to the peritoneum by means of the mucoid substance, there occurs dilatation of the vascular channels, edema, and the appearance of polymorphonuclear cells, and unidentified fixed-tissue elements. As a result of these changes, the serosa and the immediately underlying tissue lose their normal architecture and assume the appearance of granulation tissue. Within the mass, successful completion of the transformation of some of the mycelial cells into spherules takes place. Death and dissolution of the remainder occur. Polymorphonuclear cells in the vicinity of the mycotic elements also disintegrate in large numbers. The center of each mass adhering to the peritoneum becomes an amorphous area containing spherules and débris from disintegrating polymorphonuclear cells and fungus elements. The influx of polymorphonuclear cells continues. The mass, which was at first loosely adherent to the serosal surface, appears to become imbedded in the tissue. Finally the mass ruptures either into the peritoneal cavity or into the tissue. The spherules it contained readily find their way into the dilated vascular channels of the tissue; while if released into the peritoneal cavity, the fungus cells are again agglutinated and fixed to the peritoneal surface.

In the tissue proper the young spherules again attract polymorphonuclear cells. This occurs against the background of slowly developing fixed-tissue elements. If frank or microscopic suppuration does not develop, these elements later dominate the picture. It is in such an environment of fixed-tissue elements that the young spherules mature and sporulate. Larger spherules and intact sporangia of the first generation were invariably surrounded by epithelioid cells. Release of the first crop of endospores, on the other hand, again induced marked polymorphonuclear activity in the vicinity. The alternating, cyclical histologic response to coccidioidal infection in the mouse was clearly seen during the first week and corresponded with the sequence of developmental stages of the first generation of spherules, which also unfolded in orderly fashion. The peculiar property of the young spherules to attract polymorphonuclear leukocytes, and of the mature spherules to be the center of epithelioid reaction, emphasized by Forbus[20] in the examination of human material, was found to be essentially true for the mouse.

It should be noted that a small minority of spherules could be found at any stage of the infection in mice, which were of such a type as to suggest a deviation from the normal pattern of maturation. Among such aberrant forms were distorted eosinophilic spherules, some with very thick walls; others of enormous size but without any evidence of

reproductive activity; and others containing a very few gigantic endospores. The significance of these forms is not clearly understood. They may represent normal variability in the developmental cycle of *C. immitis*, or they may represent the influence of the host on the growth of susceptible cells of the parasite.

Summary

The stages by which the mycelium of *Coccidioides immitis* develops into sporangia in mice have been studied, and also the morphologic aspects of the interaction of the host and fungus after intraperitoneal injection of mycelium. Young spherules attract polymorphonuclear leukocytes, while the mature spherules become the centers of an epithelioid response. With each new generation of young spherules the suppurative reaction is revived. Thus an alternating, cyclical histologic response is found during the first week after injection. This is in accord with the nature of the tissue response to this organism in man.

We wish to express our indebtedness to Miss E. Elizabeth Tamblyn for technical assistance.

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DESCRIPTION OF PLATES

PLATE 139

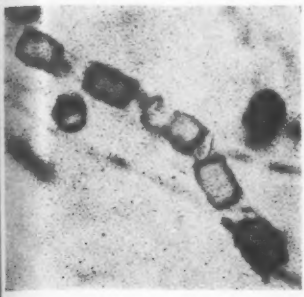
FIG. 1. Arthrospores of *Coccidioides immitis*. Wet mount.

FIG. 2. Aggregated mycelium in peritoneal smear; 20 hours, Giemsa's stain. × 250.

FIG. 3. Aggregated mycelium in polymorphonuclear mass, 24 hours. Hotchkiss-McManus's stain. × 500.

FIG. 4. Fungus cells of oval and spherical form. Peritoneal smear, 20 hours. Giemsa's stain. × 1150.

FIG. 5. Aggregated mycelium and early spherule formation in polymorphonuclear mass (detail of Fig. 3), 24 hours. Hotchkiss-McManus's stain. × 1150.



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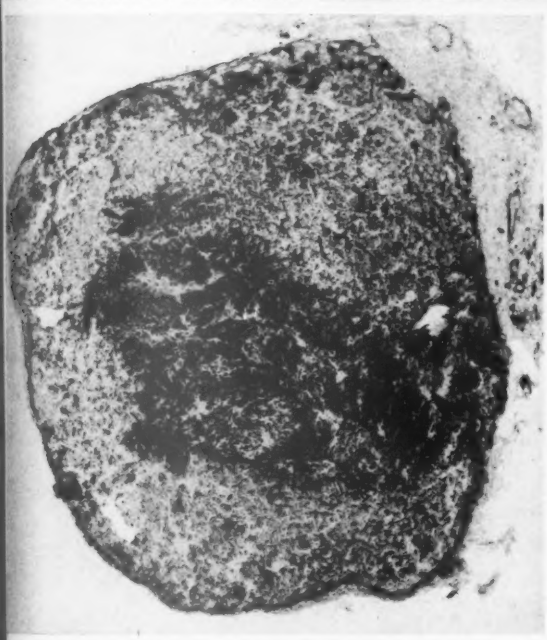

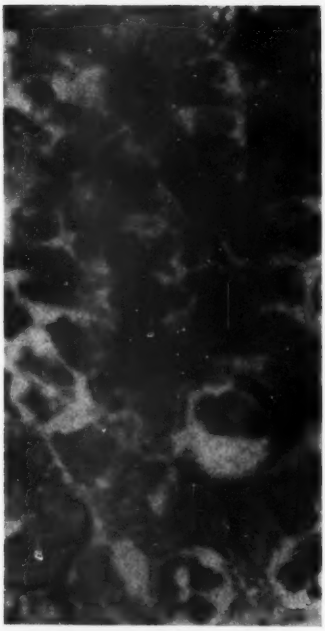

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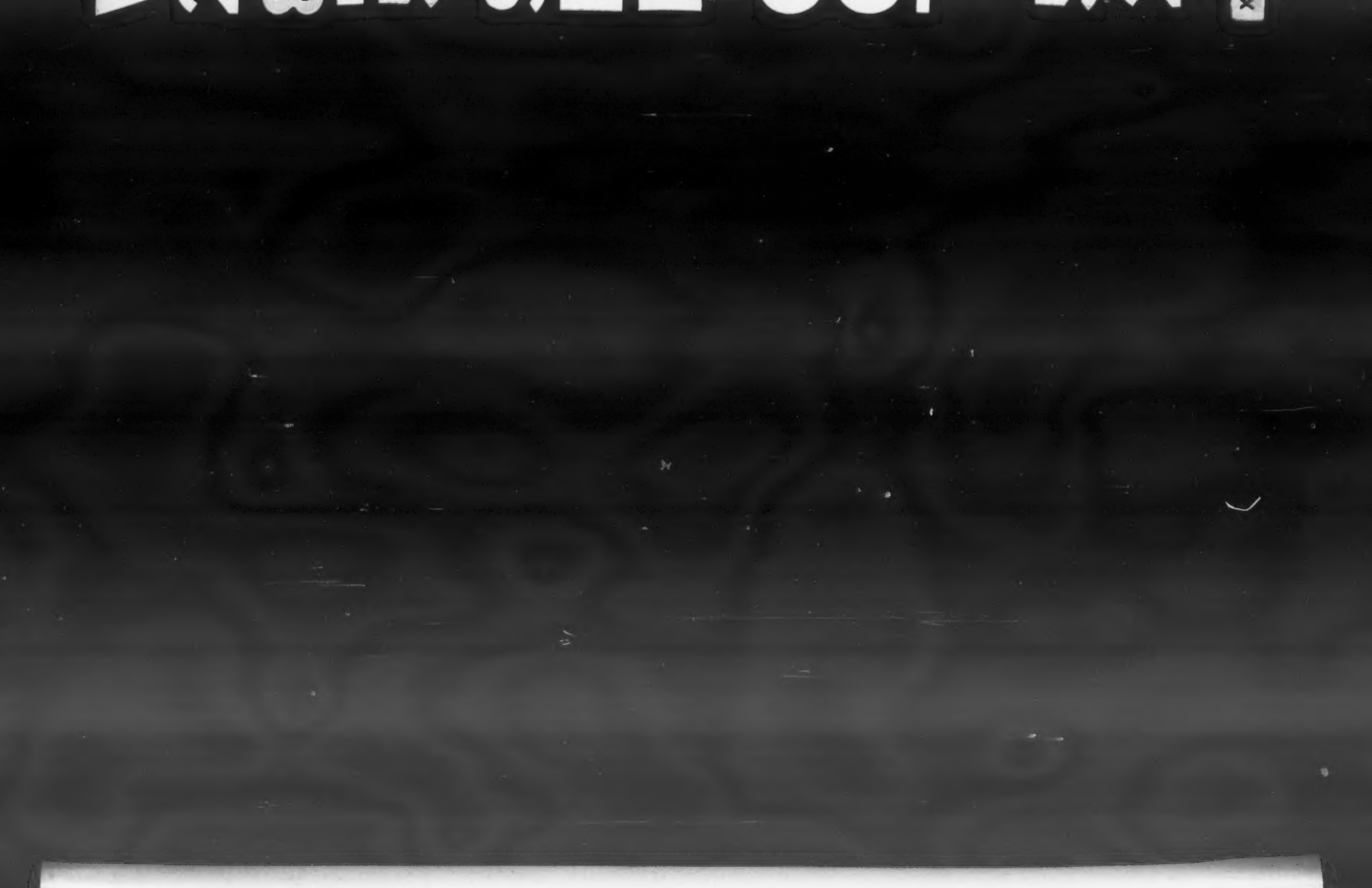
PLATE 140

FIG. 6. Polymorphonuclear aggregation containing peripheral distribution of fungus elements, 30 hours. Hotchkiss-McManus's stain. × 125.

FIG. 7. Mass containing fungus elements partially affixed to omentum, 72 hours. Hotchkiss-McManus's stain. × 125.

FIG. 8. Mass containing mycelial elements and rounded fungus cells in omentum, 96 hours. Hotchkiss-McManus's stain. × 125.



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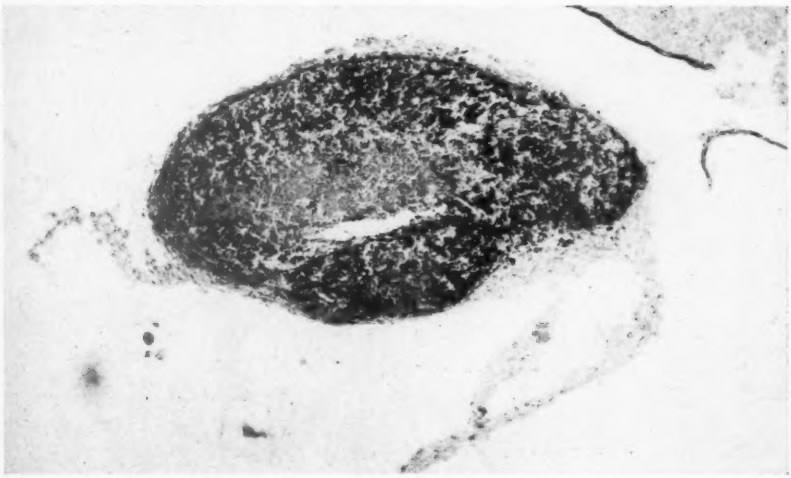

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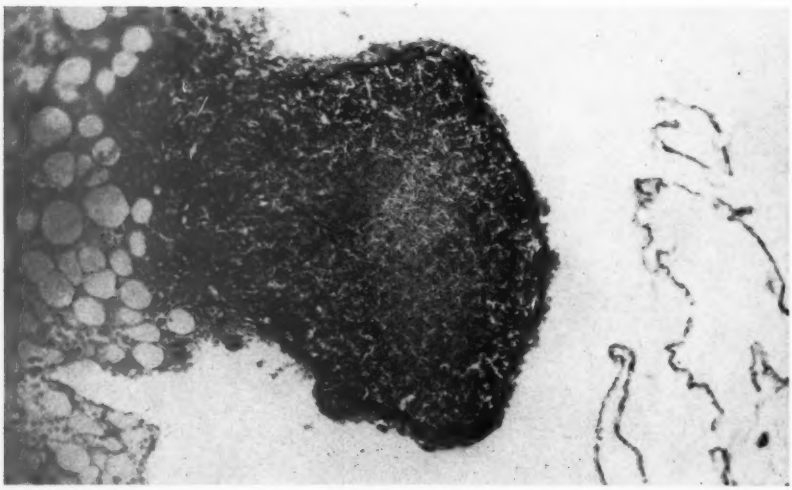

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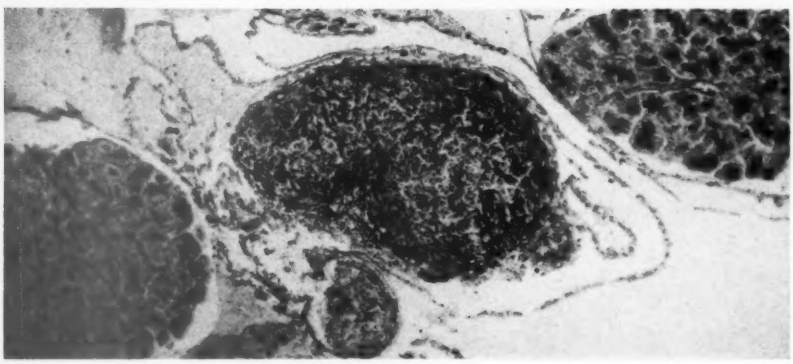

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Plate 141

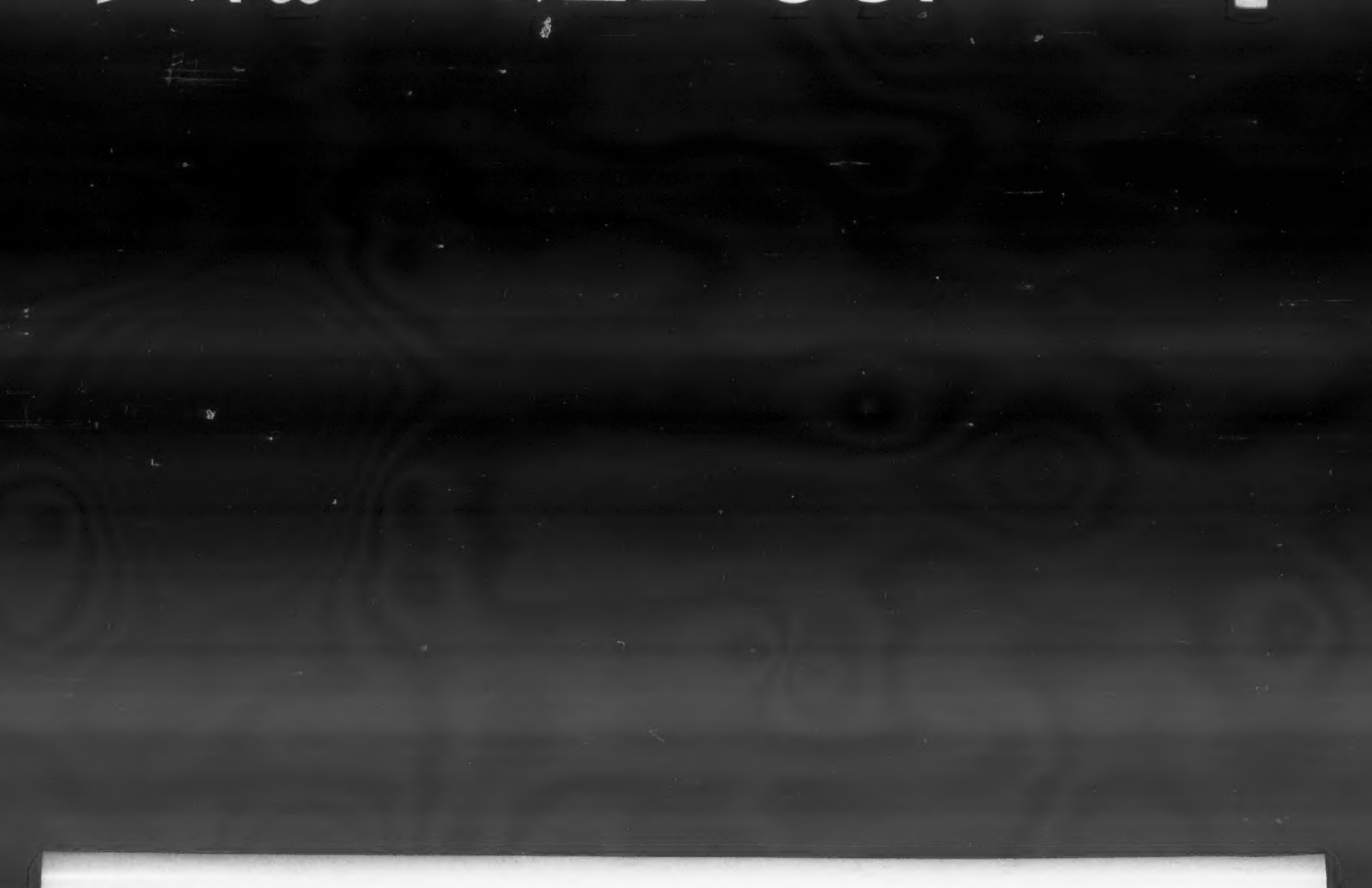
Fig. 9. Young spherules of uniform size in omentum, 4 days. Hotchkiss-McManus's stain. × 250.

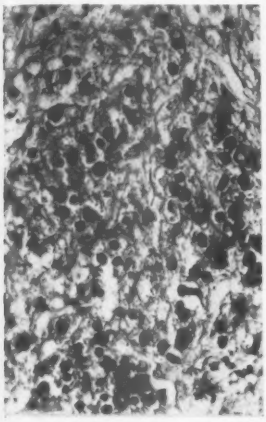
Fig. 10. Spherules in early cleavage, 5 days. Hematoxylin and eosin stain. × 250.

Fig. 11. Maturing spherules with mononuclear reaction, 6 days. Hematoxylin and eosin stain. × 125.

Fig. 12. Spherule in cleavage with mononuclear reaction, 6 days. Hematoxylin and eosin stain. × 1150.

Fig. 13. Release of endospores from mature sporangia, 9 days. Hematoxylin and eosin stain. × 250.





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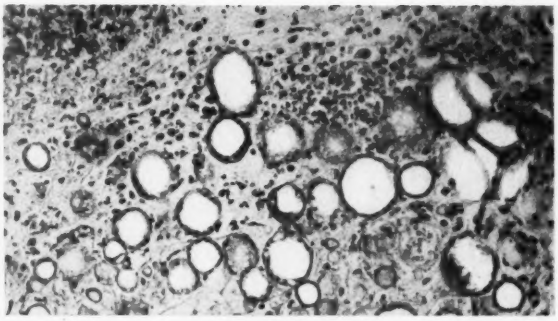

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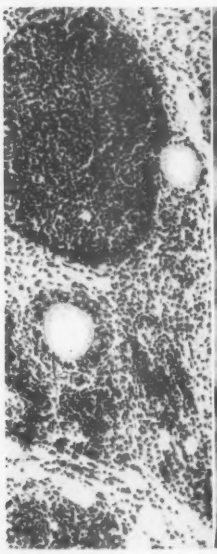

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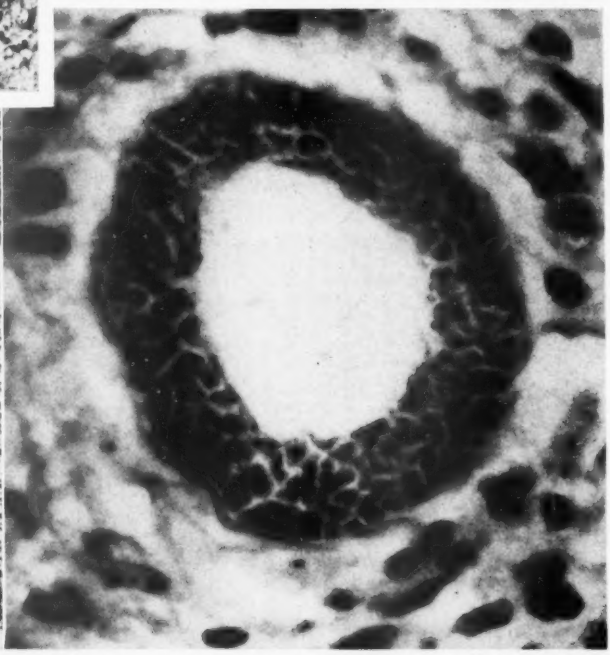

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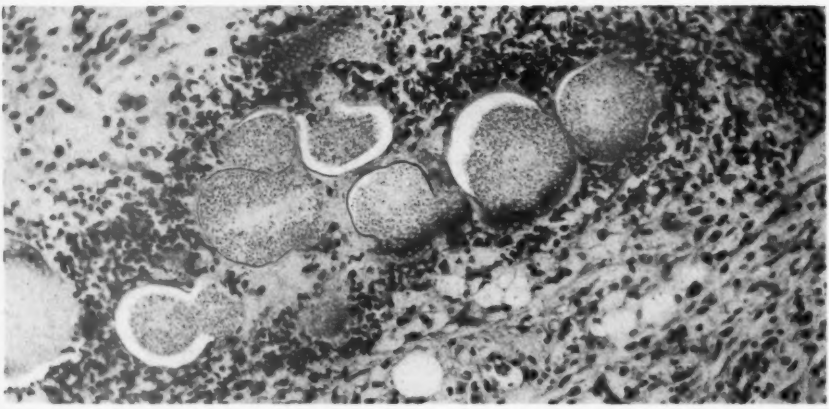

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PLATE 142

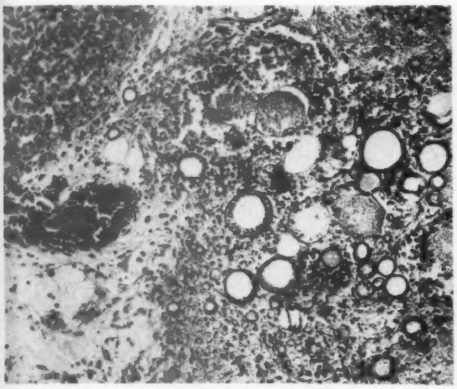
FIG. 14. *C. immitis* in mature lesion, 14 days. Hematoxylin and eosin stain. × 125.

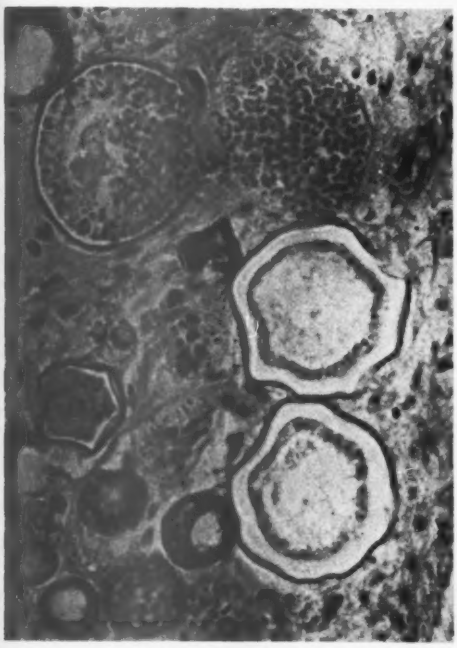
FIG. 15. Distorted, eosinophilic spherules, 12 days. Hematoxylin and eosin stain. × 500.

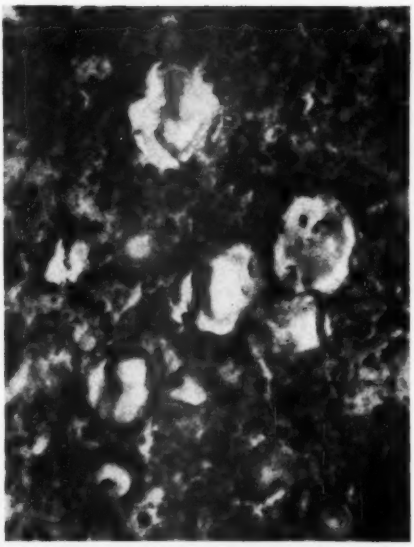
FIG. 16. Large spherules without cleavage, 20 days. Hematoxylin and eosin stain. × 600.

FIG. 17. Sporangium with small number of large endospores, 12 days. Hematoxylin and eosin stain. × 600.

FIG. 18. Sporangium with abnormally thick eosinophilic wall, 12 days. Hematoxylin and eosin stain. × 600.







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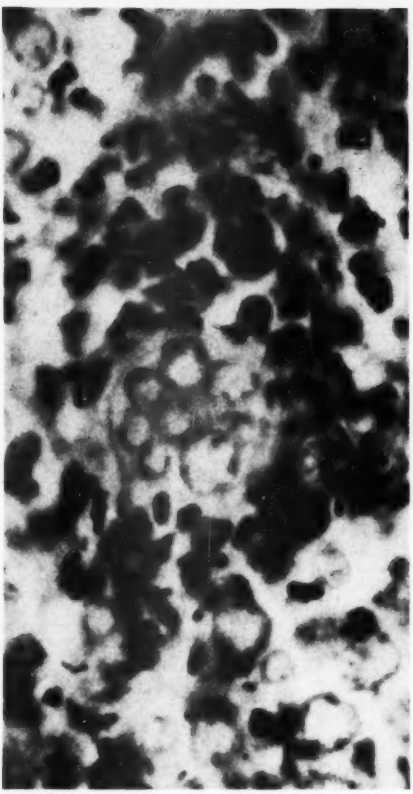

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TUBERCULOUS LESIONS OF THE CIRCULATORY SYSTEM
Report of Two Cases *

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Tuberculous lesions of the circulatory system appear to be of sufficient rarity to warrant reporting the following 2 cases. In the interval between the performances of the 2 necropsies—13 years—no similar instances were recorded at St. Elizabeths Hospital, although tuberculous involvement of other structures was relatively common. During this period 3,377 post-mortem examinations were carried out. Pulmonary tuberculosis was given as the cause of death 189 times, with involvement of other organs in 26 cases.

Rosenbaum and Linn[1] reviewed the literature of tuberculous myocarditis prior to 1948, and referred to surveys of large numbers of necropsies by Horn and Saphir[2] in 1935, and by Auerbach and Guggenheim[3] in 1937. Horn and Saphir found 19 instances in 7,683 necropsies of patients who died of generalized tuberculosis—an incidence of 0.24 per cent. Auerbach and Guggenheim reported the presence of tuberculous myocarditis in 29 cases (0.287 per cent) of 10,165 necropsies. Five more case reports appeared in the English literature in the decade following Auerbach and Guggenheim's survey. According to Beebe and Coleman,[4] who also reviewed the literature, the incidence is much higher. Hall[5] stated that about 200 cases have been reported. However, the larger figures include cases with involvement of the pericardium as well as heart muscle. Acid-fast bacilli were seldom found in the myocardial lesions.

Tuberculous arteritis is even more rare. Up to 1948, 23 cases were recorded in which the aorta was involved. Tuberculous lesions of other large arteries were recorded in 6 additional instances.

Report of Cases

CASE 1

The patient was admitted to St. Elizabeths Hospital on June 25, 1904, when he was 39 years old. He was diagnosed as having catatonic schizophrenia and showed a classical behavior pattern of that disorder. In 1922 the notes stated that he sat in the "same position and location all day, has nothing to say to anyone, nor will he answer questions.... He understands what is said to him and obeys simple commands." He showed no essential change in the following years.

In a routine roentgenogram of the chest, March 12, 1934, isolated calcified glands were observed in both lungs, but no evidence of an active tuberculous process was

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reported. There were no further roentgenograms of the chest until December 31, 1947, at which time the radiologist reported "pathology [sic] in both apices, which is probably arrested but should be surveyed." Subsequent roentgenograms showed no progression of the process. Sputum examinations in January and July of 1948 were negative for acid-fast bacilli.

When the patient was 86 years old, urethral hemorrhage was observed. He was therefore transferred to the medical service on June 22, 1951. The kidneys were not satisfactorily visualized in pyelograms and no diagnosis was derived from these examinations.

The urinalysis of June 23, 1951, was negative for albumin and sugar. Only occasional red and white blood cells were observed on microscopic examination. No pathologic organisms were cultured from a urine specimen dated June 27. In August, albumin appeared and red and white blood cells were more numerous on microscopic examinations. Occasional bacteria were noted. No acid-fast bacilli were found on smears of two catheterized specimens; however, after 35 days' culture of the first specimen, acid-fast bacilli were demonstrated.

Repeated urinalyses continued to show albumin, bacteria, and white blood cells in varying amounts. Acid-fast bacilli were found on direct smears of a catheterized specimen on October 15.

Chemical tests of the blood were repeated on numerous occasions following an initial report of non-protein nitrogen elevation to 180 mg. per 100 cc. at the time of the patient's transfer to the medical service. A few days later the non-protein nitrogen was reported as 150 mg. per 100 cc. It never reached these high levels on subsequent testing.

The blood count was within the range of normal whenever tested. Serologic tests of the blood and spinal fluid were negative.

The patient died on October 21, 1951. He was 86 years old, and had resided at the hospital for 47 years.

Necropsy Findings

Necropsy was performed 34 hours after death. Externally there was no evidence of disease, particularly no palpable lymph nodes; but the body appeared emaciated.

The heart was small and well contracted. Coronary arteries were sclerotic but not occluded. The aortic cusps and mitral leaflets were thickened slightly but the valves showed no stenosis. The myocardium was firm, pale, and free from focal lesions.

The aorta retained a mild degree of elasticity. Just above the bifurcation there was a diffuse spindle-shaped swelling, about 5 cm. in length, which was believed to be a fusiform aneurysm. On opening the vessel, however, what appeared to be a dissecting aneurysm was found. The layers of the vessel wall were separated by soft, pale brownish material mottled with whitish caseous areas. An organized, laminated thrombus filled an outpouching of the diseased wall.

Both lungs showed delicate pleural adhesions. Although the parenchyma was crepitant, numerous fine nodules were palpable bilaterally. On dissection they varied in size from 2 to 6 mm., and were pale and

firm. Caseation was not observed in these small lesions. There was moderate congestion and edema, most marked in the lower lobes. Purulent exudate was expressed from many of the small bronchioles. The main bronchi and trachea had hyperemic lining membranes. There were no emboli in the pulmonary circulation.

Small areas of focal congestion were observed in the stomach and intestines, but no trace of tuberculosis. The pancreas appeared healthy. The liver, aside from congestion, showed no visible lesions.

The kidneys were small and of decreased consistency. On the right, several rounded yellowish areas were scattered in the parenchyma. The two larger lesions were each about 1 cm. in diameter and appeared to be abscess cavities filled with soft necrotic material. No cavities were present in the left kidney in which the pale nodules were less numerous. Each kidney had a narrow cortex, fibrosis of the pyramids, and thick-walled vessels. The ureters were dilated, the right more than the left. The well-contracted bladder had a thick wall and contained soft blood clots. The mucosa was engorged and swollen, and showed focal hemorrhages. The prostate gland was hypoplastic and free from gross abnormalities. The right testicle was small and compressed by an abscess which showed a soft pale greenish center. The parenchyma of the testicle was dark. The left testis showed no evidence of an inflammatory process.

The lymph nodes were nowhere enlarged and on section appeared healthy. The spleen was small and firm; follicles were indistinct, but no lesions were observed. The endocrine system showed no evidence of disease.

The brain showed sclerotic changes of the large arteries at the base. On dissection no tuberculous lesions were observed. An old cystic infarct was found in the right corpus striatum involving a portion of the caudate nucleus and putamen and the intervening fibers of the posterior limb of the internal capsule. At the level involved in the lesion, probably only sensory fibers to and from the thalamus were interrupted. The patient showed no evidence of motor disability during his lifetime, and there is no mention in the notes of suspected cerebrovascular accident at any time. Arteriosclerosis was noted in branches of the large arteries.

Microscopic Examination

The tuberculous nature of the pulmonary lesions was confirmed. The tubercles had a characteristic structure although giant cells were not numerous. Ziehl-Neelsen staining demonstrated small numbers of

acid-fast bacilli in a few tubercles. Walls of blood vessels were infiltrated with lymphocytes and plasma cells, and larger arteries showed intimal proliferation.

A section of the aorta showed that the soft, mottled white and brown material which caused the swelling in the wall was a conglomeration of tubercles, which showed relatively large, central areas of necrosis, surrounded by lymphocytes, plasma cells, and epithelioid cells. Giant cells were numerous in the peripheral cellular zones (Fig. 1).

Various staining methods—Verhoeff's for elastic fibers, Heidenhain's and Mallory's for connective tissue, and Perdrau's for reticulum —proved that the tubercles had formed directly in the media (Figs. 1, 2, 3, and 4). The Verhoeff technic demonstrated particularly well the destruction of the elastic meshwork by the tuberculous process (Fig. 3), and the involvement of the intima in several areas. Apparently, the destruction of the intima and media by the granulomatous process had caused weakening of the wall so that an aneurysm formed, with resultant thrombus formation in the outpouching (Fig. 2). This clot was laminated.

Although much of the specimen had been discarded at necropsy, sufficient remained to permit the examination of several more areas. Tubercles were found in these sections also (Fig. 4). Acid-fast bacilli were readily demonstrated by the Ziehl-Neelsen method in sections from two areas (Fig. 5).

In addition to the tuberculous lesions, the aorta also showed sclerotic changes (Figs. 2 and 4). The intima showed focal thickening, and atheromatous and calcareous deposits. The media was largely replaced by the tuberculous lesions. The adventitia was slightly thickened and showed focal infiltration with cells characteristic of chronic inflammation generally around small vessels and nerve fibers. Rarely, small tubercles were found in this coat.

The Perdrau stain demonstrated interruption of fibrous reticulum by tuberculous granulation tissue. No reticulum appeared in the central areas of caseation. The vasa vasorum showed splitting of the elastic lamellae and intimal cellular proliferation.

In the myocardium there was a small cicatricial infarct, but no evidence of a tuberculous process. Interstitial tissue was moderately hyperplastic throughout the myocardium.

Although the liver had shown no lesions grossly, many very small, but characteristic, tubercles were scattered throughout the section. Many of them included one or more giant cells. The spleen also

showed miliary tuberculosis. Some of the Langhans cells were unusually large. Arteriosclerosis was prominent in the spleen.

In the kidney, superimposed on the damage caused by intense arteriosclerosis, there was a widespread inflammatory response, acute and chronic. There were several relatively large abscesses with clumps of bacteria which, however, were not acid-fast. (Tubercle bacilli were found on culture and direct smear from the patient's urine prior to his death.) Tubercles were observed rarely. The glomeruli showed degenerative changes of varying degrees, and many were completely replaced by hyaline scars.

The urinary bladder showed absence of mucosa with replacement by chronic inflammatory cells, and in one area, hemorrhage. Small foci of lymphocytes and plasma cells were scattered among the muscle fibers. No tubercles were observed. The prostate showed glandular hyperplasia and a diffuse chronic inflammatory reaction. In the right testis the tubules were atrophic. There was a tuberculoma in the adjacent fibrous tissue.

The endocrine organs showed no significant changes.

In addition to the cystic infarct discovered on dissection of the brain, smaller vascular lesions were observed on histologic study. A small hemorrhagic infarct was found in the thalamus in the junctional area of medial and lateral nuclei, close to the anterior nucleus, and a glial scar in the globus pallidus, adjacent to the posterior limb of the internal capsule. Blood vessels were thick-walled, particularly in the lenticular nucleus. Many of the channels in the pallidum had blue-stained deposits of pseudo-calcium in their walls. Dilated perivascular spaces were prominent around collapsed capillaries, and the parenchyma was spongy in these zones. Nerve cells of the basal ganglia showed ischemic homogeneous changes, and many contained increased lipofuscin pigment.

CASE 2

A 63-year-old obese colored female was admitted to the hospital on June 11, 1937. She had completed only 1 year of schooling, and worked as a domestic for many years. After an operation for cataracts, she became less able to care for herself and entered the Home for the Aged and Infirm. There she adjusted well for several years, but when she began to show mental confusion and wandered around the dormitory at night, she was transferred to Gallinger Hospital and then to St. Elizabeths.

On the ward she was oriented in all spheres, but showed poor insight and judgment. The conference diagnosis was psychosis with cerebral arteriosclerosis; clinical impression, syphilis. Serologic examination of the blood on June 15, 1937, was reported as anticomplimentary (Kolmer) and doubtful by the Kahn test. The Kolmer test on the spinal fluid of July 27 was reported as 2100 and the colloidal gold curve at that time, as 112322100; protein, 5 mg. per 100 cc.; and cells, 5 per cmm.

On September 7, serologic examination of the spinal fluid was reported as negative. Urinalysis gave no abnormal findings. Red blood cell count was 2,650,000 per cmm. and hemoglobin 50 per cent. The blood pressure was not elevated.

The patient was cared for on a ward for elderly patients who required much nursing attention. On several occasions she was sent to the medical service following acute attacks which the physicians diagnosed as cardiac but with no evidence of decompensation. There was no dependent edema and no cyanosis. Pulmonary symptoms were absent. Skin and the glandular, osseous, and nervous systems showed no significant changes. During her final stay on the medical service the heart beat was irregular, with no murmurs. The blood pressure was 160/100 mm. of Hg. The peripheral vessels showed marked arteriosclerosis. Electrocardiographic examinations during this period showed findings of "myocardial degeneration, arborization block and left axis deviation."

She was up each day and suffered no further acute attacks until October 31, 1938, when she vomited and had a weak pulse. She still showed no cardiac decompensation. After a few days of bed rest, she improved to her former level. On November 5 she left her bed to walk to the bathroom. She collapsed on the way and died before she could be returned to her bed.

Necropsy Findings

Necropsy was performed 7 hours after death. The body was well nourished and showed no external marks of injury or disease.

The heart, although flabby, was slightly enlarged. It weighed 435 gm. A small amount (5 to 10 cc.) of dark brownish fluid was found in the pericardial sac. The coronary arteries were thick-walled and showed numerous atheromatous, and a few calcified, plaques. They were nowhere occluded, although the left descending branch had an extremely narrow lumen in a calcified portion about 1 cm. from its origin. The thickness of the wall of the slightly dilated left ventricle was 15 mm.; that of the right, 4 mm. All valves appeared entirely normal. The myocardium was pale and turbid throughout. An extensive area of infarction occupied almost the entire intraventricular septum. The pale yellowish white lesion extended to within 4 cm. of the apex. All trace of muscle tissue had disappeared in the center of the lesion. There was a small hemorrhage in one area. The aorta showed intense atheromatous and calcareous changes.

There were bilateral pleural adhesions. The right lung weighed 630 gm.; the left, 510 gm. A firm, rounded mass about 8 cm. in diameter was found in the lower lobe of the right lung. On section the grayish white infiltrating area resembled a neoplastic process rather than a tuberculous one. The lower lobe of the left lung showed areas of fibrosis and a few small nodules. Edema was prominent throughout both lungs.

The large liver showed passive congestion. Numerous calculi were found in the gallbladder. The kidneys showed changes due to arterio-

sclerosis. There was a cyst in the left kidney. Other viscera showed no significant changes.

The brain was moderately atrophic and increased in consistency. Large vessels showed atheromatous plaques. No focal lesions were found on external examination, but on dissection after fixation, infarcts were found bilaterally in the basal ganglia.

Microscopic Examination

The lung showed extensive fibrosis and necrosis but no evidence of neoplasm. The combination of caseation necrosis and granulation tissue was considered specific for tuberculosis, although no acid-fast bacilli were demonstrated. No giant cells were observed. There was widespread infiltration with lymphocytes. Blood vessel walls were thickened and infiltrated with chronic inflammatory cells.

The myocardial lesion showed complete disappearance of muscle cells and replacement by a diffuse infiltration of chronic inflammatory cells, epithelioid cells, and characteristic Langhans giant cells (Fig. 6). The predominating cell was the plasma cell, but in some areas there were polymorphonuclear neutrophils and a few eosinophils. Peripherally, atrophic muscle fibers were separated by the reactive inflammatory cells. There was widespread increase of interstitial tissue in areas of the myocardium not involved in the granulomatous process. Although no definite tubercle formation was observed, the lesion appeared to be clearly tuberculous from the histologic picture. Ziehl-Neelsen stain, repeated on numerous occasions, failed to demonstrate tubercle bacilli.

In the liver there were many small foci of lymphocytes and a few plasma cells scattered in the parenchyma. There were no giant cells in any of these foci. The sinuses were dilated with well preserved erythrocytes but the hepatic cells showed only slight degenerative changes.

The cerebral sections showed ischemic infarcts in the basal ganglia and no evidence of syphilis or other infectious disease.

The question was raised whether the heart lesion could be a gumma since serologic tests gave doubtful indication of syphilis. The Dieterle spirochete stain was carried out on heart, lung, and liver, but no treponemata were discovered. However, a differential point in the diagnosis of tuberculosis and syphilis was noted in Hassin's[6] and Weil's[7] textbooks of neuropathology. These authors mentioned that the necrotic areas of gummata show an argyrophilic reticulum, while similar appearing necrotic areas in tuberculous lesions fail to show a

mesenchymal meshwork. The Perdrau staining method for reticulum was therefore carried out on lung and heart. There was no argyrophilic network in the large necrotic areas. If the criterion mentioned holds for areas other than the central nervous system, the diagnosis of tuberculous myocarditis was confirmed.

Discussion

In 1933 Baumgarten and Cantor[8] described an instance of tuberculous mesarteritis with aneurysm of the femoral artery. They reviewed the literature prior to their report and discovered only 20 cases of tuberculous involvement of large arteries since the first case was described by Kamen[9] in 1895. Malcolm[10] also had reported a tuberculous aneurysm of the femoral artery in 1928. Two of the other reported cases of tuberculous arteritis were in the femoral artery, one in the common iliac, one in the hepatic artery, one in the atrial appendage, and the remainder involved various portions of the aorta.

The case reported by Owens and Bass[11] in 1944 was the twenty-second instance on record of tuberculous aneurysm of the aorta. Their patient was a 72-year-old woman who had been in excellent health until 23 days before hospitalization. Constipation, anorexia, and abdominal pain were the chief presenting symptoms. During the course of her illness, there was intermittent afternoon fever, loss of weight, and falling blood pressure, which rose transiently following transfusions. Death occurred on the fourth hospital day. Numerous tests had not revealed the exact nature of her illness. Necropsy disclosed a rupture of the abdominal aorta and a huge hematoma in the right paravertebral gutter which had displaced the viscera medially. Small tubercles were found in the lungs, liver, spleen, and kidneys. The aorta showed necrosis of the media at the mouth of the aneurysm. No necrotic lymph nodes were found in the vicinity of the aorta. Microscopically, Langhans giant cells were observed in the adventitia, together with lymphocytic and plasma cell infiltration around the vasa vasorum. Acid-fast bacilli were demonstrated between the elastic fibers near the mouth of the aneurysm, and in lungs and kidneys. Owens and Bass postulated reactivation of a hilar lymph node in an elderly patient, and believed bacilli were disseminated through the blood stream from this focus, and transmitted to the media of the aorta by way of the vasa vasorum.

One more case has been reported since. Waser's[12] patient was a young man of 29 years suffering from rapidly progressing tuberculosis. At necropsy miliary tubercles were found in the lungs, liver, kidneys, adrenal glands, bone marrow, spleen, lymph nodes, heart, and aorta.

In the aorta tubercles were distributed along the intima and were readily visible grossly. There were also miliary lesions in the adventitia and in the peri-arterial tissues. Acid-fast bacilli were demonstrated in many of the lesions. Minute tubercles were scattered in the myocardium. Waser believed the lesions were established by blood-borne infection.

It is of interest that in only 4 of the reported instances were acid-fast bacilli demonstrated: those of Malcolm,[10] Owens and Bass,[11] Waser,[12] and Haythorn.[13] Some of the described examples apparently occurred as the result of direct extension from lesions in adjacent structures; in other cases an embolic origin through the vasa vasorum was hypothecated, since the tuberculous lesions were chiefly in the media.

Tuberculous involvement of the myocardium, unassociated with tuberculous pericarditis, is much more commonly encountered than granulomatous tuberculosis of the large vessels. Rosenbaum and Linn[1] stated that it may appear in three forms: miliary, nodular, and diffusely infiltrating. Their reported instance was nodular, which is the most frequently observed form. About 100 cases have been reported. The lesion of Rosenbaum and Linn was in the interauricular septum. The patient, a man 21 years of age, was discovered to have pulmonary tuberculosis in January, 1947. Symptoms of meningitis developed in March; this was proved to be tuberculous. He received extensive treatment with streptomycin. There were no symptoms referable to the circulatory system, except a fall in blood pressure during the last few days of life. The patient died on July 22, 1947.

Necropsy showed tuberculosis of lungs, kidneys, leptomeninges of brain and cord, and myocardium. Acid-fast bacilli were demonstrated in smears from caseous areas in the heart lesion.

In their review of the existing literature, Rosenbaum and Linn[1] found the right side of the heart to be involved more frequently than the left. The route by which the tuberculous lesions in the myocardium became established has not been proved definitely. The authors believed that a hematogenous route might be responsible for a miliary spread, but not for a single large tuberculoma. The lymphatic route has been favored by the majority of observers, and Rosenbaum and Linn believed this the logical mode of spread for isolated tuberculomas.

The tuberculous lesions of the myocardium reported by Rauchwerger and Rogers[14] were on the left; the largest tuberculoma at the base of the mitral valve was 2 cm. in diameter and yet had caused no clinical evidence of heart disease. Two slightly smaller tuberculomas were in the wall of the left atrium. Characteristic tubercles were found in the lungs, spleen, liver, intestines, lymph nodes, and on the surfaces

of the kidneys; and there were large areas of caseation in the adrenal glands. The bodies of all of the spinal vertebrae showed caseous necrosis, which was most intense in the thoracic region where a large cold abscess had developed.

The majority of the reported cases have been without signs of cardiac disease; the authors[14] found only 5 in which symptoms of cardiac distress were noted. Case 2 in this presentation is thus the sixth on record.

The patient reported by Beebe and Coleman[4] is one of those with cardiac symptomatology. In August, 1941, she had a bundle branch block, but was not decompensated. About 1 year later symptoms of coronary occlusion developed 5 days after a radical mastectomy had been performed. On her final hospitalization in November, 1942, there was again evidence of partial atrioventricular and intraventricular block. Numbness, cyanosis, and anesthesia of the feet developed, and then gangrene. The patient died on the 21st day of hospitalization. The heart showed marked chronic fibroplastic myocarditis, mural thrombosis of left and right ventricles; thrombosis of the aorta, right and left common iliac, external and internal iliac, and femoral arteries, and small branches of the pulmonary arteries. There was also a chronic fibrous tuberculosis of the lungs and calcification of tracheobronchial and parabronchial lymph nodes. Histologic examination confirmed the tuberculous nature of the lesions in the lungs and lymph nodes, and showed a chronic fibrous tuberculosis of the myocardium. The giant cells contained stellate refractile inclusions surrounded by vacuoles, but no acid-fast bacilli were found. No mention is made of histologic study of the thrombi in the various vessels, although the authors believed that emboli released from the mural thrombi on the endocardium were responsible for the development of the numerous thrombi.

In my case 1 it is noteworthy that the patient had recognizable, but apparently quiescent, lesions in the lungs for many years before involvement of the genito-urinary system manifested itself a few months before death. Probably there was reactivation of the primary focus in the lung. The aorta and kidneys were already damaged by arteriosclerosis and thus it is probable that the bacilli were able to set up new foci in structures weakened by disease. Whether aortic or renal involvement came first can only be speculated.

It has been stated that aortic aneurysms in the lower abdomen generally do not give rise to symptoms. However, in the patient described by Owens and Bass,[11] persistent abdominal pain was the chief presenting symptom. This was probably due to the pressure of the hematoma resulting from the ruptured aorta.

In case 2 the tuberculous lesion appeared to be of the diffuse type. The lung was the only other organ involved. The scattered foci of inflammatory cells in the liver were of doubtful etiology. While the mediastinal lymph nodes were slightly enlarged, they were grayish black on section and appeared entirely healthy. All other lymph nodes were inconspicuous.

Since the tuberculous lesions in the aorta and heart were unexpected findings on histologic study in both cases, additional lymphatic structures were no longer available. Consequently, no discussion of the mode of dissemination (hematogenous or lymphogenous) can be undertaken. The disseminated miliary lesions in the liver and spleen in case 1 suggest a hematogenous route. Furthermore, the distribution of tubercles in the media of a vessel has been considered proof by Baumgarten and Cantor[8] that the dissemination of the bacilli is hematogenous, by way of the vasa vasorum in the involved arteries, especially when no directly adjacent structures to the involved portion of the vessel showed tuberculous lesions.

Summary

Two cases of pulmonary tuberculosis were found to have concomitant tuberculous lesions in the circulatory system. In case 1 there were tubercles in the aorta, confirmed by the demonstration of acid-fast bacilli; in case 2, there was a tuberculous granulomatous lesion in the myocardium (interventricular septum).

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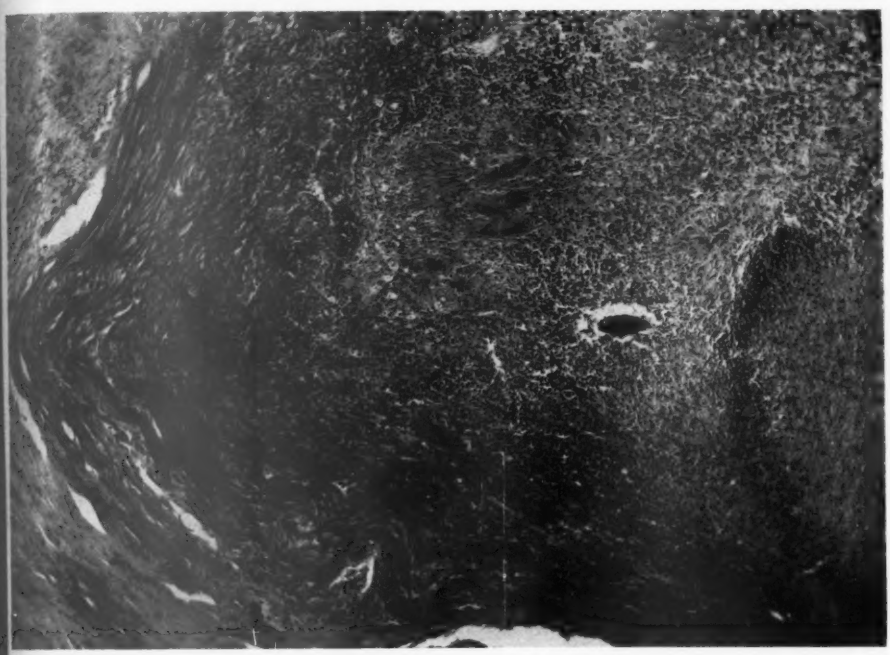
DESCRIPTION OF PLATES

PLATE 143

FIG. 1. Case 1. Higher magnification of an area in Figure 2. Tubercle formation with giant cells. Verhoeff's elastic fiber stain. × 103.

FIG. 2. Case 1. Tubercle formation in the media at the edge of the aneurysm in which there is thrombus formation. Atheromatosis of intima. Verhoeff's elastic fiber stain. × 21.

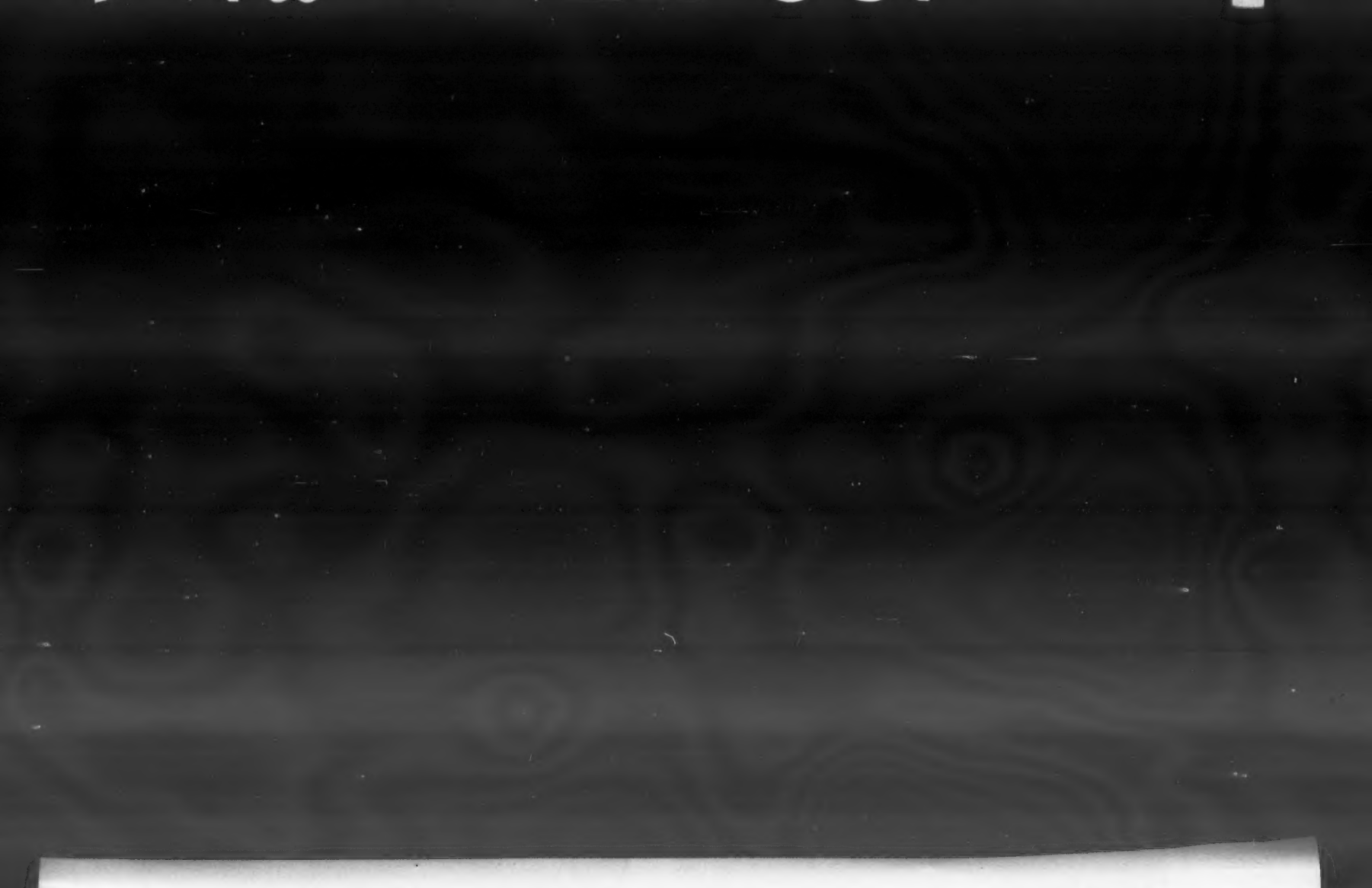


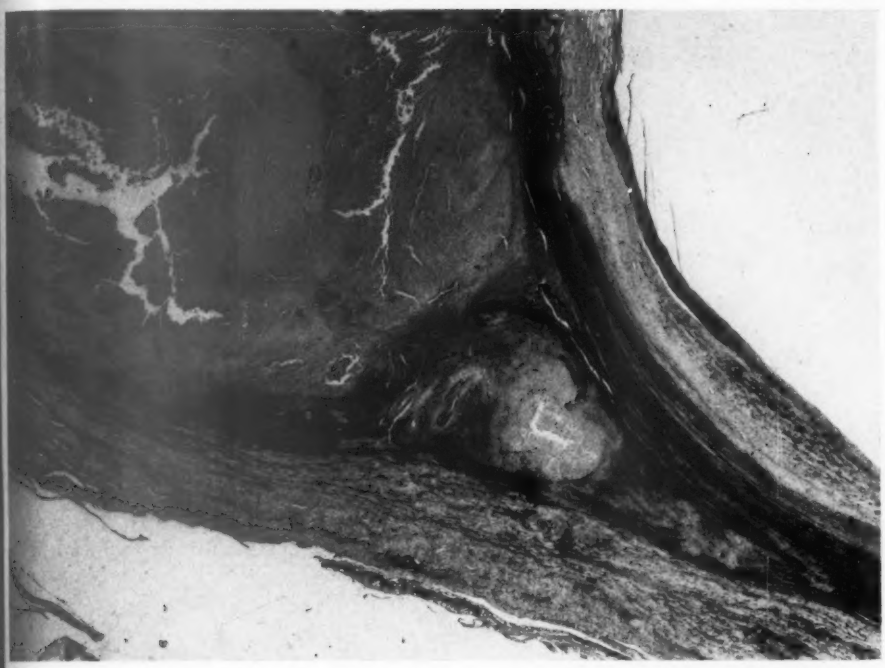
Neumann Tuberculous Lesions of Circulatory System

PLATE 144

FIG. 3. Case 1. Tubercle formation in the media. Atheromatosis of intima, and thick-walled vasa vasorum in adventitia. Verhoeff's elastic fiber stain. × 21.

FIG. 4. Case 1. Interruption of elastic lamellae of media by tuberculous process (detail from Fig. 3). × 103.





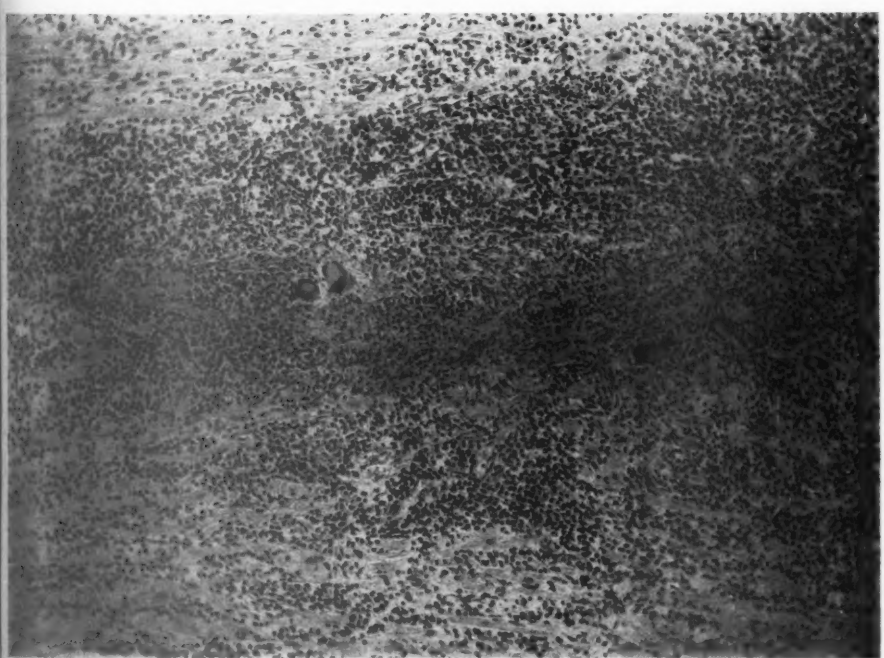
Neumann Tuberculous Lesions of Circulatory System

PLATE 145

FIG. 5. Case 1. Acid-fast bacilli in an area of tuberculous necrosis in the aorta. Ziehl-Neelsen stain. × 560.

FIG. 6. Case 2. Tuberculous granuloma with giant cell formation in the myocardium. Hematoxylin and eosin stain. × 103.

Neuma



Neumann Tuberculous Lesions of Circulatory System

STRUCTURAL ALTERATIONS WITHIN THE AORTIC INTIMA IN INFANCY AND CHILDHOOD*

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Arteriosclerosis in young persons has been reported with increasing frequency in recent years. The most comprehensive study of juvenile arteriosclerosis is that of Zeek[1] who reviewed the world literature up to 1930. She collected 98 necropsied cases of patients under 20 years of age, but stated a complete survey was impossible since so few examples were listed in the medical indexes under either arteriosclerosis or vascular disease. One-half of the total number of cases in that report occurred during the age period from 10 to 14 years, with 6 cases less than 1 year old and 10 cases between 1 and 4 years of age. The survey included the aorta and peripheral and visceral vessels, but apparently was concerned only with atherosclerotic lesions. While no one condition stood out prominently enough to signify etiologic value, the infectious diseases were the most common cause of death, although Zeek hastened to add that such is also the case without arteriosclerosis.

Willius and Smith[2] studied the incidence and degree of coronary and aortic sclerosis in 5,060 consecutive post-mortem examinations. In the age group from 0 to 9 years of age the coronary arteries revealed grade I sclerosis in 10.2 per cent, and grade II sclerosis in 0.2 per cent. Similarly in the same age group the aorta disclosed grade I in 23.2 per cent, grade II in 0.5 per cent, and grade III in 0.2 per cent. Unfortunately, the histologic criteria for this grading were not stated nor was there any description of the pathologic changes or correlation with the cause of death.

The development of early and often severe arteriosclerosis in diabetic children has long been recognized. Warren,[3] who studied the incidence of arteriosclerosis by decades in diabetic patients, stated that no arteriosclerosis was observed in 9 cases from 0 to 10 years, while there was a 41 per cent incidence in 17 cases between 11 and 20 years of age. Likewise xanthomatosis, another systemic pathologic condition associated with a disturbance in cholesterol metabolism, has been shown to be fatal in very young children by reason of its effects on the vascular system.[4] That juvenile arteriosclerosis, even in the absence of metabolic disorders, may be progressively fatal is attested to by

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French and Dock's[5] analysis of 80 fatal cases of coronary arteriosclerosis in soldiers ranging from 20 to 36 years of age.

While all the instances cited refer to the atherosclerotic variety of arteriosclerosis in children and young adults, there have also been several reported examples of a very unusual type of arterial disease apparently limited to infants.[6-8] The affected vessels, including the aorta, revealed calcium deposition in relation to the internal elastic membrane with an associated intimal fibroblastic proliferation. The etiology of this condition has not been satisfactorily explained and it seems to have no counterpart in adult arterial disease.

Our interest in juvenile arterial disease was stimulated by the accidental finding of microscopic areas of intimal thickening in routine blocks from infants' aortas. Nothing unusual had been noted on gross examination of the aorta so that the location and extent of these changes could not be determined. Dock[9] described similar intimal changes in the coronary arteries of infants, terming them intimal cushions, and stated that the increased severity of the process in the male might be an explanation for the difference in sex incidence of coronary occlusion in later life. Fangman and Hellwig[10] confirmed's Dock's observations but believed that these thickenings represented the earliest stages of intimal atherosclerosis rather than an inherited anatomical peculiarity. Several questions presented themselves concerning this intimal change in the infant's aorta, *i.e.*, relative frequency, location, sex incidence, cause of death, histopathologic changes, progression, and possible relationship of this lesion to atherosclerosis.

Material and Method

In an attempt to clarify these problems, the aortas from 50 consecutive pediatric necropsies were studied. The entire length of the aorta was preserved and fixed in 10 per cent formalin. Serial blocks were taken in a transverse plane at 0.5 cm. intervals and numbered consecutively from the aortic valves to the bifurcation of the iliac arteries. Using this technic, the number of blocks varied from 10 to 57, with an average of 25 per case. A variety of staining procedures was used, including hematoxylin and eosin, Verhoeff's elastic stain, Mallory's phosphotungstic acid hematoxylin stain, Wilder's stain for reticular fibers, Masson's trichrome stain, buffered toluidin blue for evidence of metachromasia, and a periodic acid, silver, methenamine stain.[11] No attempt was made to correlate the findings with the clinical data until the study was completed.

Clinical Data

Twelve cases showing an unusual intimal thickening were encoun-

tered among the 50 aortas studied. Some of the data relevant to these children are collected in Table I. While this represents an incidence of 24 per cent, it must be pointed out that the figure has little significance in view of the peculiar age scatter. Thirty-nine of the total died within the first 2 weeks of life, the majority being either stillborn or premature infants, and in this group only one case was encountered. This was a premature infant of 7½ months' gestation who died on the first

TABLE I

Summary of Cases of Aortic Intimal Hyperplasia

Case no.	Necropsy no.	Age	Sex	Cause of death	No. of plaques	Location of plaques
1	A51-80	1 day	M	Prematurity (7½ months)	1	Low thoracic
2	A51-82	5 weeks	M	Atresia of ileum	1	Low thoracic
3	A51-3	6 weeks	M	Asphyxia from formula aspiration	2	Arch Lumbar
4	A50-104	10 weeks	M	Internal hydrocephalus, meningomyelocele	1	Arch
5	MPA51-40	3 months	M	Biliary duct atresia, biliary cirrhosis	1	Low thoracic
6	MPA51-22	6 months	M	Embryonal hepatoma with metastases	2	Low thoracic Lumbar
7	MPA51-39	6 months	M	Meningo-encephalitis	3	Arch and thoracic Lumbar (2)
8	MPA51-41	8 months	M	Biliary duct atresia, biliary cirrhosis	1	Lumbar
9	A51-17	17 months	M	Bronchopneumonia	1	Low thoracic
10	MPA51-34	8 years	M	Amyotonia congenita, bronchopneumonia	3	Low thoracic (2) Lumbar
11	MPA51-46	8 years	F	Skull fracture, subdural hematoma, contusion of brain	2	Mid thoracic Lumbar
12	MPA51-19	14 years	F	Rheumatic heart disease, subacute bacterial endocarditis	3	Arch Thoracic Lumbar

day of life. Each of the remaining 11 necropsied infants, ranging from 5 weeks to 14 years, showed evidence of intimal change. Although 10 of the 12 cases occurred in males, no conclusions can be drawn regarding sex incidence because so few female children in the older group were studied.

Considerable variation in the cause of death is apparent. Infectious disease accounted for 4 deaths while liver and biliary duct abnormalities were the cause of death in 3 cases. It is unfortunate that blood cholesterol levels were not determined in the latter.

The site of the intimal thickenings was determined and this is of interest because, in general, the distribution tended to correspond with that noted in atherosclerosis of later life. The numbers in parentheses

indicate that more than one focus of thickening was found within the area listed. Although lesions were observed in the arch, the thoracic and lumbar areas were the more frequently affected. It is of interest that these thickenings tended to be located on the posterior aortic surface.

Review of the family history of these infants disclosed no findings judged to be of significance.

Pathologic Findings

The intimal coat of the infant aorta is normally a very simple structure, being composed of a single layer of endothelium which appears to lie directly upon a prominent internal elastic membrane. Early in life there is formed a subendothelial zone consisting of branching elastic tissue, collagenous fibers, smooth muscle, and a few wandering cells. This is such a slowly progressive and uniform change throughout the vessel length that this layer normally has assumed little prominence even at puberty.

Bremer[12] has pointed out that mesenchymal differentiation appears at widely different periods in embryonic life in different arteries and is usually accompanied by a narrowing of the vessels as the circulation becomes more definite. Persistence of this mesenchyma-like structure was invariably noted in our study within the intima and inner media of the innominate, left common carotid and left subclavian arteries at birth, and for a considerable length of time thereafter (Fig. 1). This change is emphasized because similar intimal and medial changes were observed within the aortic arch adjacent to the point of origin of these three vessels (Fig. 2), and could readily be differentiated from the intimal lesion which will be described. Another aortic intimal structure which must be distinguished from pathologic intimal hyperplasia is the small elastic tissue elevations which are located just proximal to the origin of all aortic branches. These structures are well developed at birth, show no evidence of degenerative change in later life, and are recognized by their characteristic shape, location, and abundant elastic tissue (Fig. 3).

The changes with which this paper is concerned are entirely intimal, extending from the endothelial lining to the internal elastic membrane, and were not visible on gross examination. When viewed as a true cross section, these intimal thickenings were conchoidal and occupied one-fourth to one-half of the aortic circumference. Although there was variation in thickness, the plaques were generally between one-half and three-fourths the thickness of the underlying media. It is of interest that there was no correlation between age and degree of intimal

thickening, some of the examples of more marked thickening occurring in the younger infants. Despite the fact that the transition from the plaque to the normal intima was gradual, nothing unusual was noted within the intima adjacent to these thickenings (Figs. 4 and 5). The individual plaques were elongated in the longitudinal axis of the aorta and varied in length from 0.5 to 4.5 cm., with an average of 1.5 cm.

The endothelium over the affected areas revealed an apparent increase in the number of cells with cytoplasmic swelling and prominent vesiculation of their nuclear structure. Many of the cells were arranged tangentially and occasional cells appeared to be in a plane perpendicular to the luminal surface. Necrosis of the endothelium with deposition of a thrombus on the injured surface over the plaque was noted in cases 7, 9, and 12, all of these presumably being associated with bacteremia. Directly beneath the endothelium and comprising the main structure of the plaque was a pale-staining connective tissue matrix in which the only cellular elements appeared to be of fibroblastic origin. With the use of appropriate stains, much of this acellular material was shown to be elastic tissue (Fig. 6), and was distributed generally as a delicate network, although some relatively coarse fibers were present. The elastic tissue appeared to be of maximum density in the mid-portion of the plaque, with decreasing amounts as one approached either the endothelial layer or the internal elastic membrane. The latter structure was thickened in the region of the plaque and consistently showed focal loss of ability to stain a homogeneous black with Verhoeff's technic. In addition, it failed to show the usual undulatory appearance and seemed flattened, with indistinct margins, fragmentation, fraying, and disintegration of structure. At no point was there any evidence to suggest that the intimal elastic fibers described were arising from the internal elastic membrane. The remainder of the non-cellular material comprising this intimal thickening consisted of an extremely delicate meshwork of collagenous fibrillar material and small amounts of metachromatic staining material as demonstrated on formalin-fixed tissue with a buffered toluidin blue stain. The metachromatic substance was noted chiefly beneath the hyperplastic endothelial cells and in that portion of the intima which was in contact with the internal elastic membrane. It is of interest that this mucopolysaccharide substance was not present to a significant degree within the unaffected intima, although large amounts were noted within the interlamellar spaces of the media.

The cellular elements within the plaque, previously mentioned as fibroblastic in origin, were arranged generally in a plane parallel with the endothelial surface. Altschul,[13] who studied these cells, pointed out

that they have been variously interpreted as proliferated endothelial cells, peculiar migratory smooth muscle cells, and fibroblasts. He preferred the term intermediate since he believed dedifferentiation has usually not gone far enough to permit one to recognize their source.

The cells within the intimal thickenings were characterized by stellate eosinophilic cytoplasm with fibroblast-like multipolar processes. The cell nuclei were spindle or oval, vesicular, and although double nuclei were occasionally seen, mitotic figures and well defined nucleoli were not noted. The periodic acid, silver, methenamine stain, with which collagen fibrils and basement membranes stain dark gray to black, demonstrated each cell to be invested with a very thin cuticle of connective tissue substance. Embedded in this were many black fibrils which extended along the cytoplasmic processes and finally branched away to anastomose with fibrils of nearby similar cells (Fig. 7). Fibrils within the cuticle were sometimes seen in cross section so that it took on a beaded appearance. With Verhoeff's elastic stain some of the fibrils appeared to be elastic and were arranged in a loose, irregular network. The Masson trichrome stain showed no evidence of myofibrils within the cytoplasm of these cells. With the phosphotungstic acid hematoxylin stain a delicate blue pericellular cuticle with a few blue-staining, fine fibrils running along these cells was seen. The periodic acid silver stain revealed this cuticle and the fine, blue-staining fibrils seen with phosphotungstic acid hematoxylin were stained black. These blue staining fibrils were called fibroglia by Mallory[14] who stated they were most numerous in young rapidly growing connective tissue and that they differed chemically from collagen and elastic fibrils. It is our opinion that the periodic acid, silver, methenamine stain demonstrates this cuticle and that embedded within it are fine collagen fibrils. Whether a small percentage of these fibrils embedded in the cuticle are fibroglia or not is not known. Elastic tissue as seen in stains for elastica appears as a tangled network but its exact relationship to the cuticle of these cells is incompletely understood. We think that these cells are fibroblasts and that the periodic acid, silver, methenamine stain gives the most precise detail of this intimal cell.

Medial and adventitial abnormalities were not observed in any of the cases herein reported. Very little attention was directed toward other vessels in these children although the iliac arteries were examined in the majority of cases. Plaques similar to those within the aorta were not seen, although one instance of true medial calcification was noted in case 1 (Fig. 8). This was a premature infant of 7½ months' gestation, who expired on the first day of life and both iliac arteries were affected.

Discussion

The sequence of events which occurs in the development of the atherosclerotic plaque is incompletely understood. Much of the present-day investigation has been concentrated upon the rôle and manner of deposition of lipids while the more basic processes such as intimal fibrosis, hyalinization, and calcification have been largely ignored. This attitude has been due chiefly to the experimental production of atherosclerosis by the administration of cholesterol to a variety of animals. Although most investigators caution against drawing too close an analogy between lesions of experimental and human atherosclerosis, the majority admit that there are striking similarities at the so-called fatty stage of the lesions. The technic followed in our study did not permit the use of fat stains but others have noted minute amounts of lipid within similar plaques in young persons. Lev and Sullivan[15] stated that in some foci of aortic endarteriosclerosis, fat is deposited in the ground substance, muscle fibers, and elastic fibers, and that these fat accumulations become larger with age, forming elevated zones. Although we did not see macrophages in any of our cases, Lev and Sullivan noted these secondarily, with a marked increase in collagen fibers even later. Similarly, Fangman and Hellwig,[10] in their study of cushion-like elevations in the coronary intima of newborn infants, found lipid deposits along the elastic fibers, in the stroma of the cushions, and sometimes within large histiocytes.

Although not a part of the present study, we have recently encountered in 2 very young persons fatty and calcific aortic plaques of grossly typical adult type. The first child was 10 years of age and died as a result of chronic glomerulonephritis (Fig. 9), and the other was 16 years old and died from chronic rheumatic heart disease (Fig. 10). Microscopic examination revealed plaque-like elevations which were strikingly similar to those herein described. There was, however, in these 2 cases, focal necrosis of the fibro-elastic tissue, and the appearance of lipid-containing macrophages was a conspicuous feature. Karsner[16] accepted the opinion that the first change in arteriosclerosis is damage in the lower intima with splitting of elastic fibers, some destruction of fibrous connective tissue and even of muscle, and deposit of lipids. In response to this injury connective tissue then is formed in excess to produce intimal plaques. Since it is our impression that the lesions we have described in these 12 children may be an early phase in the development of the adult atherosclerotic plaque, a few comments on the possible genesis of this lesion in children may be warranted. The first stage is undoubtedly concerned with the action

of some injurious agent, as yet unknown, upon the subendothelial fibroblasts and adjacent internal elastic membrane. The latter structure manifests this by fraying, fragmentation, and the loss of ability to take a deep elastic stain. This injurious effect results in an excessive reparative process by the occasional subendothelial fibroblasts which proliferate and deposit successive layers of elastic tissue and loose collagen fibers. Subsequently the connective tissue cells apparently degenerate, disappear, and at the same time hyalinization of the connective tissue fibrils occurs. Concurrently, lipidic substances accumulate and excite the migration of macrophages into the area to phagocytize this foreign material. Dystrophic calcification is prone to occur in any such necrotic fatty area.

While the relationship of elastic tissue to the formation and development of the atherosclerotic plaque is not clear, certain observations may be pertinent. Blumenthal, Lansing, and Gray[17] pointed out that elastic tissue breakdown and its subsequent calcification may predispose the vessel to intimal plaque formation. Using the micro-incineration technic, they showed that in the aorta and in renal, iliac, and hepatic arteries, calcification is intimately associated with alterations in the physical character and pattern of distribution of elastic tissue. Furthermore, they stated that the intensity and rate of calcium deposition are directly proportional to the intensity and rate of elastic tissue changes. The data of Blumenthal, Lansing, and Wheeler[18] regarding the age incidence of aortic medial calcification show an incidence of medial calcification prior to 20 years of age of only 4 per cent, with an increase to 58 per cent in the group between 20 and 30 years of age. Quantitative analysis of the medial elastic content of the human aorta by these same investigators revealed average elastin content of over 48 per cent in the first 2 decades of life, while in the third decade and thereafter decrease to values between 41.1 and 44.1 per cent was observed.[19] Our observations regarding intimal elastic tissue in children cause one to speculate that, had this elastic content study been extended to include the aortic intima, equal or even more marked changes of a similar trend might have been noted.

Summary

The entire length of the aorta from 50 routine necropsies on infants and children was studied in an effort to determine the frequency, age incidence, location, and histologic pattern of intimal fibrous thickenings which were not visible on gross inspection of the aorta. Fibroelastic plaques were found in one of 39 infants less than 2 weeks of age and in each of the remaining 11 children ranging from 5 weeks to

14 years of age. Because the contours and the anatomical location of these plaques corresponded so closely to the lesions of adult atherosclerosis, it is postulated that these intimal thickenings may represent the earliest phase in the development of the adult lesion.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

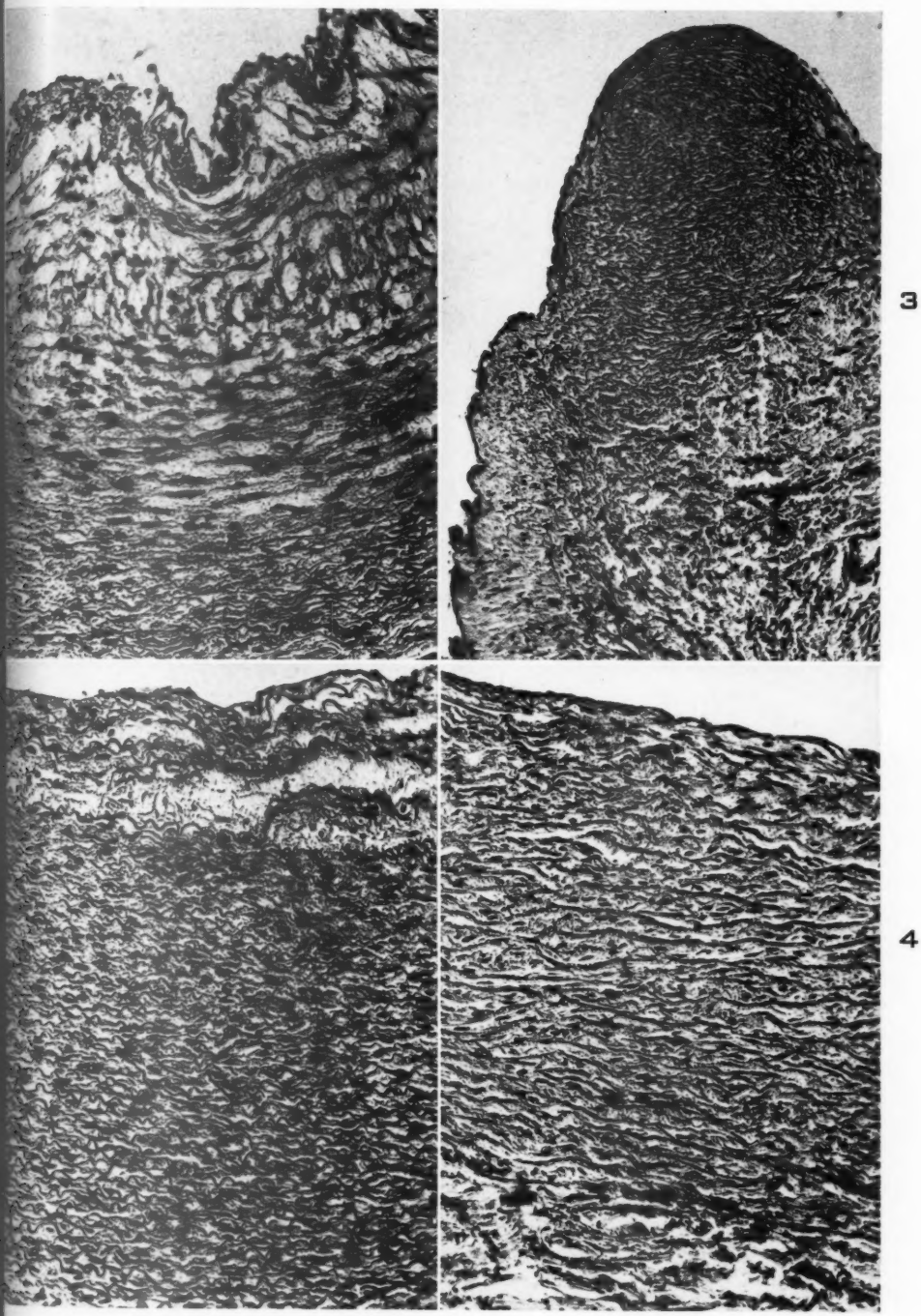
PLATE 146

FIG. 1. Innominate artery from a 2-day-old child. The loose mesenchymal structure of the intima and inner media is apparent. × 175.

FIG. 2. Aorta at a point adjacent to the origin of the innominate artery of the same infant used for Figure 1. Intima of this character was present constantly in the aortic arch and can be differentiated from true fibro-elastic hypertrophy. × 175.

FIG. 3. Normal elastic intimal hillock noted just proximal to all aortic branches. × 100.

FIG. 4. Case 7. Normal aortic intima at a point opposite thickening shown in Figure 5. × 175.



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Prior and Jones Aortic Intima in Childhood

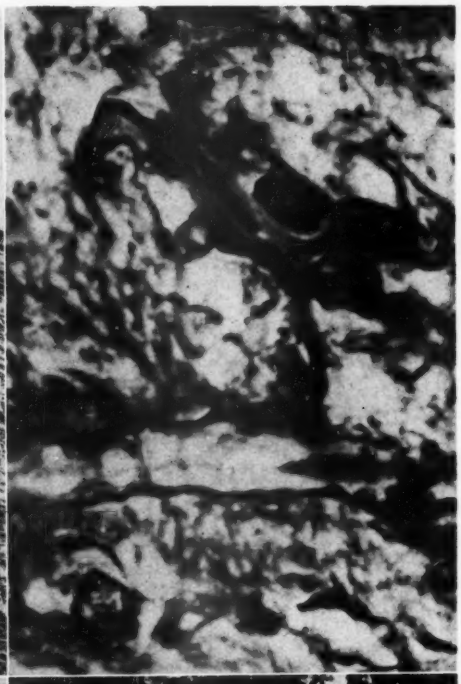
PLATE 147

FIG. 5. Case 7. Intimal fibro-elastic plaque at a point opposite normal intima of Figure 4. Fraying and splitting of the internal elastic membrane is apparent. × 175.

FIG. 6. Case 10. Elastic stain of an intimal plaque. Changes within the internal elastic membrane are particularly prominent. × 175.

FIG. 7. Case 11. Silver-positive filamentous processes radiating from an intimal fibroblast within a plaque. × 1725.

FIG. 8. Case 1. Calcification within the media of a common iliac artery. × 175.



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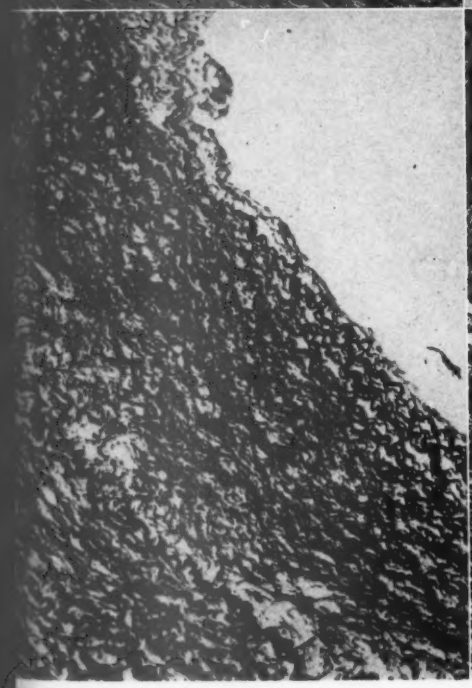

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Prior and Jones Aortic Intima in Childhood

PLATE 148

FIG. 9. Entire length of aorta from a 10-year-old male dying from chronic glomerulonephritis.

FIG. 10. Aorta from a 16-year-old-male dying from chronic rheumatic heart disease. The arch is above.

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10

Prior and Jones Aortic Intima in Childhood

"UNTREATED" BRONCHOGENIC CARCINOMA
A Report of Thirty-five Cases *

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The natural course of tumors of a designated type and site is the best yardstick for evaluating the effects of definitive therapy in tumors of like kind and origin. When such data become available, it will not be necessary to wait a specified number of years (*e.g.*, 5) in order to determine the comparative effectiveness of any given method of treatment. In any case it is wasteful to wait as long as 5 years when one deals with tumors as apt to be rapidly fatal as bronchogenic carcinomas, even though a few patients with cancer of the lung sometimes live several years after the diagnosis has been established.[1,2] For these occasional cases, data based upon total biologic behavior are as valid as those obtained by following groups of patients for a set term of years, unless that term is longer than the survival period of the exceptionally long-lived few. The practice of administering one of the recently discovered chemotherapeutic agents for inhibiting the growth of tumors[3] and/or palliative x-ray therapy is so nearly universal that it is becoming increasingly difficult to find groups of cases of untreated cancer. It is hoped that our report will stimulate others to institute similar studies in order that statistically acceptable data may be accumulated for each decennial period, wherewith to compare the results of definitive treatment.

Methods, Material, and Results

General

Our material was selected from the records of 906 patients who were necropsied at the Veterans Administration Hospital, Louisville, Kentucky, from the time it opened, April 1, 1946, until December 31, 1951. During this period there were 1509 deaths in the hospital. The 35 cases constitute 11.47 per cent of 305 malignant tumors, and 55.55 per cent of the bronchogenic carcinomas in our necropsy material (Table I). Our necropsy material is fully representative of the fatal illnesses which occurred during the period of 69 months covered by this study, every effort having been made to obtain consent for postmortem examination on all patients who died in the hospital. Failure

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to obtain consent was and still is made the subject of inquiry. The viscera were examined and sectioned in all but 6 instances. (In one of these, examination was restricted to removal of the kidneys; to the cranial contents in the other 5.) The brain was not removed routinely, but only when there was some suspicion of an intracranial lesion. (The brain was examined in 21 of the 35 cases included in this study.) Tissue sections were prepared from the somatic organs in every case, even though they appeared normal when examined grossly. Additional sections were prepared, when this seemed advisable, from wet stock material which is saved routinely on every necropsy. The clinical rec-

TABLE I

Annual Admissions, Deaths, and Necropsies from April 1, 1946, to December 31, 1951; the Number and Percentage of All Malignant Tumors, Proved at Necropsy, Total Number of Bronchogenic Carcinomas, and of Those with No Definitive Treatment

Year	Admissions and readmissions	Total deaths				Total necropsies		Total malignant neoplasms*		Bronchogenic carcinomas		Untreated bronchogenic carcinomas	
		Medical	Surgical	Neuro-psychiatric	Total	Number	Percentage of deaths	Number	Percentage of all necropsies	Number	Percentage of all cancers	Number	Percentage of all cancers of the lung
1946†	4190	80	24	3	107	57	53	18	32	2	11	2	100
1947	9489	149	65	1	215	148	69	42	28	13	30	5	38
1948	9460	166	81	19	266	156	59	54	34	9	16	5	55
1949	8903	196	92	14	302	180	60	58	32	14	24	8	57
1950	8460	209	105	20	334	174	52	56	32	10	17	8	80
1951	5635	193	83	9	285	191	67	77	40	15	19	7	46
Totals	46137	993	450	66	1509	906	60.0	305	33.6	63	20.6	35	55.5

* This includes "lymphomas," leukemias, Hodgkin's disease, gliomas, and occult carcinomas.

† Nine month period, April 1 to December 31.

ords of all cases of bronchogenic carcinoma in our necropsy material were scrutinized carefully so as to exclude any in which definitive therapy had been instituted. In addition to several which had been treated more actively, 4 cases were discarded because palliative x-ray therapy had been administered terminally to 2 patients, and the other 2 died less than 2 months after undergoing exploratory thoracotomy. (Actually, it is not considered likely that the course of the disease was modified materially by these procedures, but the possibility that it might have been could not be eliminated with certainty.) An exploratory thoracotomy was performed in 10 of the 35 patients selected for this study. However, the operative procedure was not extensive in

any, and was followed by prompt recovery in all. There was nothing to indicate, either clinically or pathologically, that the operation shortened the life of any of these patients, all surviving 8 months or more. The remaining 25 patients were not operated upon. All 35 received transfusions of whole blood and antibiotics, as indicated for anemia or infection, respectively. The considerable difference in the incidence of carcinoma of the lung in our necropsy material and that found by Ariel and associates[4] is difficult to explain. Their patients, like ours, necessarily were more than 18 years old and there was as marked a preponderance of males at Hines Hospital as at ours. It is probable that the relative incidence of bronchogenic carcinoma at this hospital has been in excess of what it will be within a few years, chiefly because the number of patients with carcinoma of the stomach, colon, and rectum seen at necropsy has been surprisingly small to date. When these reach a "normal" incidence, the relative percentage of bronchogenic carcinoma will drop accordingly, in agreement with recent reports.[5-9]

The annual admissions varied but little for the years 1947 to 1950, inclusive (Table I). During those years the hospital had a bed capacity of 1,000, whereas it operated at a capacity of only 500 during most of the 9-month period for 1946. In 1951 the capacity was reduced gradually to 500 beds, thus accounting for the drop in total admissions. The higher death rate during 1951 is attributed to the circumstances that, as the capacity of the hospital became more limited, admissions had to be restricted to applicants obviously in need of immediate care, with a corresponding reduction of those needing elective care.

The relatively large number of necropsies performed on patients with malignant neoplasms is due to two factors: (1) It is easier to obtain consent for necropsy when death is due to cancer than to other diseases. (2) This hospital has been designated a tumor treatment center and many patients with an established diagnosis of malignant disease are referred for therapy.

Classification

We classified our cases as follows:

Epidermoid carcinomas	18
Anaplastic carcinomas	13
Mixed (epidermoid and gland cell) carcinomas	2
Adenocarcinomas	1
Terminal bronchiolar (diffuse alveolar)	1
Total	35

This classification includes all but the "bronchial adenomas" and conforms to the nomenclature favored by others.[10-14] According to general experience, as well as ours, there is close correlation between the histologic differentiation of carcinomas of the lung and their clinical behavior,[5,6,8,15,16] although Henkin[17] could not establish any consistent differences in the clinical course or site of predilection of metastases in tumors of the various histologic categories. It is important that tissue sections should be adequate and fully representative, because variations in structure due to necrosis, chronic inflammation, and compression are common and may obscure cytologic structure. Our 2 cases listed as "mixed" contained foci of poorly defined but recognizable epidermoid cells and groups of adenomatous cells growing freely within the affected lung. These are not regarded as due to the growth of 2 primary tumors, but as evidence of anaplasia or de-differentiation.[18] Olson[15] and Reingold and his associates[9] also noted a small number of cases which were difficult to classify because of admixtures of epidermoid and gland cells. It seems logical to adopt a descriptive name for tumors of this type, although their small number, like that of the adenocarcinomas and the terminal bronchiolar type, excludes them from further consideration in this study.

Spread

The extent of spread of the tumors (Table II) was determined by following certain arbitrary standards. When involvement was limited to the ipsilateral lung, it was listed as being confined to a single struc-

TABLE II

Correlation Between Histologic Type and Number of Structures Involved

	Epidermoid (18)	Anaplastic (13)	Mixed (2)	Adeno-carcinoma (1)	Terminal bronchiolar (1)
One structure	3	3	0	0	0
Two structures	4	2	1	1*	0
Three structures	2	1	0	0	1†
Four structures	2	4	0	0	0
Five or more structures	7	3	1	0	0

* The one case of adenocarcinoma involved the brain.

† The one terminal bronchiolar carcinoma involved both lungs, equally and diffusely, and metastasized to regional lymph nodes.

ture, even though the pleura of the same lung was implicated. When the cancer extended to the mediastinum, the pericardial surface of the heart, or any one of the mediastinal structures beyond the pleura, it was listed as involving two structures. The two epidermoid carcinomas which invaded three structures were still confined to the chest

cavities (lung, peribronchial lymph nodes and wall of the esophagus, respectively), whereas in the case of the single anaplastic carcinoma in this category, metastases were noted also in sections of the pancreas. In every instance in which involvement could be demonstrated in four or more structures, the carcinoma extended beyond the thoracic cavities, both in the epidermoid and in the anaplastic types. While there was some correlation between the type of carcinoma and extent of spread, the epidermoid were almost as prone to extend outside the

TABLE III

Correlation Between the Types of Carcinoma and the Structures Involved in Their Spread

	Epidermoid (18)	Anaplastic (13)	Mixed (2)	Adeno-carcinoma (1)	Terminal bronchiolar (1)
Regional lymph nodes	16	5	2	0	1
Mediastinal structures	9	6	1	0	0
Contralateral lung	6	2	0	0	1
Retroperitoneal lymph nodes	5	0	1	0	0
Liver	4	5	1	0	0
Kidney	4	2	0	0	0
Mesenteric lymph nodes	2	1	0	0	0
Adrenal gland	2	7	1	0	0
Pancreas	0	6	0	0	0
Brain	2	6	1	1	0
Cervical lymph nodes	3	1	0	0	0
Axillary lymph nodes	1	0	0	0	0
Thyroid gland	2	1	0	0	0
Bones	3	2	0	0	0

thoracic cavities as were the anaplastic tumors (50 and 54 per cent, respectively). This is in accord with the report of Henkin[17] who noted that "the different histological categories . . . . metastasize in a similar manner," but is contrary to the experience of others.[2,10,11,13,14] It is possible that in our cases the life of the host was prolonged by the liberal use of antibiotics and transfusions of whole blood. By thus inhibiting infection and anemia, the cancer has more time to complete its biologic course.

When the different structures in which neoplastic tissue could be demonstrated are listed in relation to the histologic classification of the carcinoma, important differences become evident in the behavior of epidermoid as contrasted with anaplastic carcinomas (Table III). Involvement of the regional lymph nodes could be demonstrated in 16 of the 18 epidermoid cancers, but in only 5 of the 13 anaplastic ones. The epidermoid tumors generally showed a significantly greater tendency to invade the adjacent structures of the mediastinum, the con-

tralateral lung, and distant lymph nodes than did the anaplastic cancers. Many of the latter tended to invade the adventitia of the thoracic aorta, spreading thence to the celiac axis and to the pancreas and adrenal glands. To our knowledge, this explanation for the frequent involvement of the pancreas and adrenal glands has not been suggested previously. Studies are now being undertaken to determine how often this method of spread can be demonstrated. The anaplastic tumors also metastasized readily to the brain but the route of spread to the latter could not be determined. It is possible that cerebral involvement was secondary to embolic neoplasia of the paravertebral vessels, but this was not investigated specifically. The demonstration of widespread metastases in squamous cell carcinomas of the lung is contrary to the experience of Bogardus and his associates,[10] although our cases nearly paralleled his with respect to the frequent involvement of mediastinal structures by epidermoid tumors and extensive dissemination of the anaplastic ones to somatic organs. Gebauer[13] and Koletsky[14] both reported diffuse, vigorous but non-selective spread of the anaplastic tumors, in contrast to the more deliberate growth of the epidermoid ones. Samson,[16] on the other hand, reported that the anaplastic carcinomas seldom spread to distant organs by the hematogenous route. As will appear later, we attach considerable significance to this section of our study, believing that it should determine whether resection, in a given case, is for "cure" or for "palliation." A real need exists for additional data relating to this phase of the biology of lung tumors and their proclivity for colonization in distant organs.

While there is some difference of opinion regarding the extent and manner of spread of the various types of bronchogenic carcinoma, observers generally agree that they do tend to metastasize electively, according to cell type.[9,11,15] Involvement of the adrenal glands, pancreas, brain, and liver occurred with striking frequency in our cases of anaplastic carcinoma (Table III). Jaffé[5] also noted the affinity of bronchogenic carcinomas to metastasize to the perigastric and the peripancreatic lymph nodes, pointing out that this may result in compression and distortion of the stomach, thereby leading to an erroneous diagnosis of carcinoma of the stomach. This occurred in 9 of the 100 cases in his series. The need for *awareness* of the propensity of bronchogenic carcinomas to masquerade as tumors primary in distant organs has been stressed repeatedly but not sufficiently. Two of the patients in our series were admitted with a diagnosis of probable brain tumor.

Clinicopathologic Correlation

Data concerning the age at onset of symptoms, their duration, the size of the tumors, and the possible etiologic significance of repeated

infection of the upper respiratory passages are listed in Table IV. It is apparent that epidermoid carcinomas tend to occur at a significantly later average age, start more insidiously, and run a more protracted course than the anaplastic tumors. This gives rise to the clinical anomaly that tumors which arise "explosively" and apparently some-

TABLE IV

Clinicopathologic Correlation

Type of carcinoma	Total cases	Age at onset of symptoms					Duration of symptoms in months					Largest diameter in cm.			Relation to repeated upper respiratory infections	
		Indeterminate	40–49	50–59	60–69	70 plus	Indeterminate	0–6	7–12	13–24	25–36	Indeterminate	2–5	More than 5	Apparent	Non-apparent
Epidermoid	18	2	2	7	6	1	2	6	3	6	1	5	5	8	9	9
Anaplastic	13	0	2	10	1	0	0	10	2	1	0	2	7	4	2	11
Mixed (Epidermoid and adenocarcinoma)	2	0	1	1	0	0	0	1	0	1	0	1	1	0	1	1
Adenocarcinoma	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	1
Terminal bronchiolar	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1

what recently, may be much more widely disseminated than others which, judged by patients' histories, seem to have been neglected. The slower evolution of the epidermoid carcinomas is reflected also in their larger average size at necropsy. These differences are real and significant. The patient has time to adjust himself to changes brought on by the slow growth of the epidermoid tumor and, as a rule, does not feel greatly inconvenienced or complain much until the tumor encroaches upon neighboring structures or causes bronchostenosis with secondary bronchiectasis and infection. The rapidly growing anaplastic tumors, on the other hand, do not permit of such gradual adjustment and possibly are composed of cells with a greater inherent capacity for invasive growth and metastatic dissemination. We could find no significant evidence that repeated upper respiratory infections predispose to the development of bronchogenic carcinoma. In any case, a history of recurrent infection is of diagnostic value only in so far as it may direct attention to the presence of a probable pulmonary lesion.

Correlation of the data listed in Tables II, III, and IV permits certain conclusions: A bronchogenic carcinoma which is bulky and has invaded the regional lymph nodes is not necessarily beyond hope of cure by resection. Contrariwise, a small and seemingly "recent" can-

cer may be incurable because of extension to the adventitia of the aorta and metastases in the abdominal viscera. The *probability* of cure by radical operation should be predictable in a majority of bronchogenic carcinomas by examination of sections prepared by frozen section technic. It has been our experience that sections satisfactory for rapid diagnosis can be prepared fairly easily in the case of epidermoid carcinomas and adenocarcinomas. The cells of the anaplastic tumors are more apt to "drop out" so that it is technically more difficult to obtain good sections from them. But even this negative evidence may be turned to advantage by an experienced observer. In such cases an opinion of probable anaplastic carcinoma can be rendered with some confidence.

A list of the presenting symptoms which were observed most commonly in our cases is recorded in Table V. Similar symptoms have

TABLE V

Correlation Between Important Presenting Symptoms and Type of Carcinoma

Symptoms	Epidermoid (18)	Anaplastic (13)	Mixed (2)	Adeno-carcinoma (1)	Terminal bronchiolar (1)
Cough	7	5	1	0	0
Dyspnea	7	4	0	0	1
Pain in chest	6	3	0	0	0
Loss of weight	6	3	1	0	0
Hemoptysis	2	4	0	0	0
Terminal status on admission	0	1	0	1	0

been noted repeatedly by others.[6,7,11,19] Henkin[17] divided the presenting symptoms into four groups, according to whether they were due to pulmonary involvement, metastases to bones, brain, or other organs. A two-fold division of symptoms—those due to pulmonary involvement and those due to distant metastases—might be preferable. These various signs and symptoms are so similar to those associated with pulmonary disease of much less significance that every medical student and every physician should remember these slightly paraphrased aphorisms: Cyclic recurrence of fever, leukocytosis, and anemia may be a signal indicating periodic necrosis of bronchogenic carcinoma, *not* one of recurrent pneumonia;[17] and, a change in the nature of a cough, not merely chronic cough, may be a herald of cancer of the lung.[19] In the final analysis, the diagnosis of bronchogenic carcinoma depends upon awareness of its likelihood[8] and utilization of every diagnostic aid.[8,20] Correct diagnosis by roentgenographic means varies within

wide limits, according to recent reports,[8,11,17,20] but probably does not exceed 75 per cent of all cases, including those in an advanced stage of the disease. Diagnosis by bronchoscopic examination probably is successful in an even smaller number of cases according to some,[8] or to about an equal degree according to others.[20] The increasing willingness of surgeons to urge exploratory operation is justified by the facts that it is difficult to diagnose cancer of the lung by other means, and the operation is attended by relatively slight risk of mortality or prolonged morbidity.[8,20] Moreover, this is the only means by which the chances for cure can be ascertained.

Summary and Conclusions

A study has been presented of the necropsy findings in 35 cases of untreated bronchogenic carcinoma.

The bronchogenic carcinomas in this series were divided into five groups, according to their histologic appearances: epidermoid, anaplastic, adenocarcinoma, mixed epidermoid and adenocarcinoma, and terminal bronchiolar.

Significant differences were demonstrated in the behavior and course of epidermoid carcinomas, as contrasted with those of anaplastic type.

The epidermoid carcinomas, in our series, arose more insidiously, grew more slowly, and started at a later average age than the anaplastic. The epidermoid carcinomas electively metastasized to the regional lymph nodes but also spread diffusely. Five or more organs were involved in 7 of the 18 cases in our series. The suggestion is advanced that this was due to prolonging the life of the host by transfusions of whole blood and use of antibiotics, thus affording the epidermoid tumors more time and a better opportunity for distant spread.

The anaplastic carcinomas started at an earlier average age than the epidermoid. They often arose "explosively," invaded the adventitia of the thoracic aorta, and metastasized to the pancreas and adrenal glands by way of the celiac axis and other branches arising from the aorta. They also electively metastasized to the brain.

Presenting symptoms are not sufficiently distinctive to permit of differentiating bronchogenic carcinoma from common pulmonary disease due to other causes. The triad of fever, leukocytosis and anemia, occurring in cycles, and a change in the nature of a cough are significant symptoms suggestive of bronchogenic carcinoma.

Histologic examination of tissue taken for biopsy and prepared by frozen section technic may be of considerable prognostic value in determining whether a radical resection offers hope of cure.

The demonstration of metastases in the regional nodes, in cases of

epidermoid carcinoma, is not necessarily an indication of incurability. With anaplastic carcinomas, attention should be directed to evidences of invasion of the adventitia of the thoracic aorta. If this is present, the probability of involvement of the pancreas and/or adrenal glands is increased materially.

There is need for additional studies of this type and pooling of the data so acquired.

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